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Review Article

Hemidesmus indicus (Sariva): A Systematic Scoping Review of Phytochemistry, Traditional Ayurvedic Knowledge, and Preclinical Evidence in Cancer Research

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Abstract:

Tumours frequently resist mono-targeted therapies, necessitating the exploration of multi-target botanical drugs. *Hemidesmus indicus (Sariva)* is a prominent plant traditionally prescribed in Ayurveda for blood diseases, systemic inflammation, and neoplasms. Since its oncological potential remains fragmented across various models, this systematic scoping review maps traditional Ayurvedic knowledge against modern phytochemical and preclinical evidence to comprehensively evaluate its anticancer efficacy and highlight critical research gaps. Following PRISMA-ScR guidelines, a systematic literature search identified *in vitro, ex vivo,* and *in silico* studies investigating the anticancer, antileukaemic, and anti-angiogenic effects of *H. indicus.* Extracted data encompassed cancer types, botanical parts, and molecular mechanisms. Seven principal preclinical studies met the inclusion criteria. The root phytocomplex, dominated by benzaldehydes, demonstrates synergistic broad-spectrum cytotoxicity across leukaemia, colorectal, breast, and lung cancer models. Mechanistically, it induces intrinsic and extrinsic apoptosis, enforces cell-cycle arrest, and uniquely overcomes leukaemic differentiation blocks. Furthermore, it acts as an "endogenous vaccine" by triggering immunogenic cell death (ICD) via DAMP (damage-associated molecular patterns) mobilisation and starves solid tumours by inhibiting angiogenesis. Additionally, aerial flavonoids like rutin computationally exhibit superior targeted inhibition of breast cancer receptors. The phytocomplex also exhibits a dual paradox: genoprotecting healthy DNA from mutagens while exerting pro-oxidant lethality in tumours. *H. indicus* possesses robust multi-target anticancer efficacy that molecularly validates its traditional Ayurvedic uses. However, clinical translation

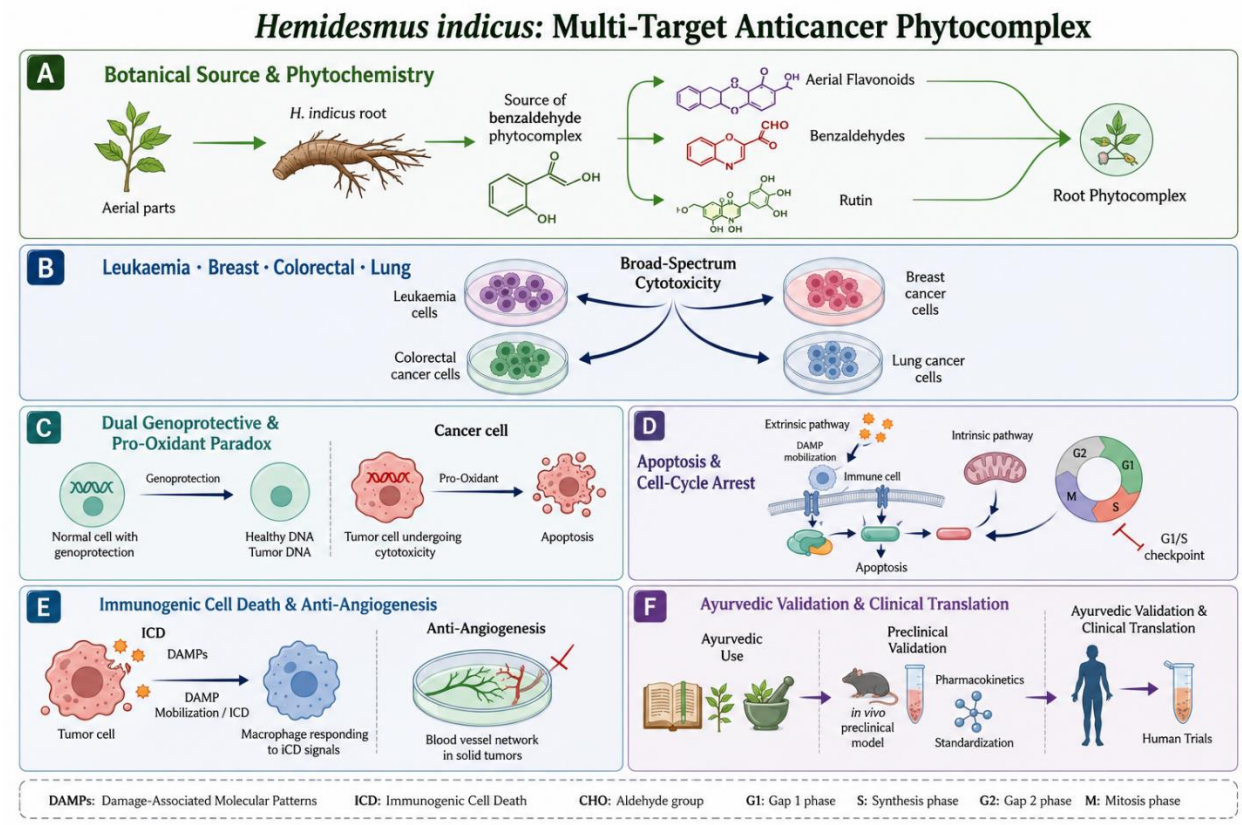
necessitates rigorous *in vivo* validation and human trials to confirm systemic safety, pharmacokinetics, and standardisation.

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Graphical Abstract



1. Introduction

Cancer is a highly complex disease characterised by multiple genetic and molecular alterations that involve the deregulation of cell proliferation, apoptosis, angiogenesis, and invasion [1]. Because of this profound biological diversity and the redundant nature of aberrant cellular signalling pathways, tumours frequently develop adaptive resistance to mono-targeted therapies [2]. Consequently, there is a paradigm shift in modern oncology towards multi-targeted therapeutics capable of simultaneously disrupting multiple critical nodes within the cancer network. In this context, botanical drugs and natural plant products have emerged as highly promising candidates due to their intrinsic complexity, which allows them to interact with numerous molecular targets and modulate diverse biochemical cascades simultaneously. Acknowledging this potential, the United States Food and Drug

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Administration (FDA) has approved botanical prescription drugs composed of complex natural mixtures, validating that such plant-derived therapies can meet rigorous clinical and quality-control standards [3].

Among traditional Indian medicinal plants, *Hemidesmus indicus* (L.) R. Br. (Apocynaceae), commonly known as Indian Sarsaparilla or *Sariva*, holds a prominent position. According to traditional Ayurvedic knowledge, the plant is classified as a *Rasayana* (a rejuvenating medicine) and its roots are widely prescribed as a decoction for the treatment of numerous systemic ailments. Traditional therapeutic indications specifically include the management of *Raktavikara* (blood diseases), *Daha* (fever and inflammatory conditions), *Visha* (poisoning), *Agnimandya* (dyspepsia), *Shwasa* (dyspnea), *Atisara* (diarrhoea), and *Pradara* (menorrhagia), etc. [4]. Furthermore, traditional medical practitioners actively employ polyherbal formulations containing *H. indicus* for the direct treatment of neoplasms and cancer.

Modern phytochemical evidence has characterised the chemical fingerprint of *H. indicus* root extracts, identifying and quantifying principal bioactive phytomarkers such as 2-hydroxy-4-methoxybenzaldehyde (MBALD), 3-hydroxy-4-methoxybenzaldehyde, 2-hydroxy-4-methoxybenzoic acid, and vanillic acid. Further phytochemical mapping reveals the presence of flavonoids (such as rutin and quercetin) heavily concentrated in aerial parts, alongside complex terpenoids and alkaloids throughout the plant [5]. Crucially, while isolated principal constituents (e.g., MBALD) exhibit potent antioxidant properties, they demonstrate only weak direct inhibition of cancer cell proliferation and fail to independently induce apoptosis [6]. The profound anticancer and genoprotective properties of the plant rely heavily on the synergistic interactions of the entire phytocomplex, demonstrating a necessary "matrix effect" for its multi-target efficacy.

Recent preclinical experimental evidence has begun to provide robust pharmacological validation for the plant's traditional oncological uses. *In vitro, ex vivo,* and *in silico* studies demonstrate that *H. indicus* extracts possess broad-spectrum cytotoxic, cytostatic, and anti-angiogenic activity across colorectal, breast, hepatic, lung, and leukaemic cancer models [6]. Despite the compelling convergence of traditional Ayurvedic indications and modern molecular validation, significant research gaps restrict the translation of *H. indicus* into clinical oncology. The current body of anticancer evidence remains strictly preclinical, heavily restricted to in vitro isolated cell cultures and computational simulations. There is a pronounced lack of rigorous in vivo animal studies and human clinical trials to confirm systemic therapeutic efficacy, safety, and bioavailability. Furthermore, unpredictable drug-drug interactions with conventional chemotherapies and the exact signalling pathways driving its phytocomplex synergy remain unmapped. Therefore, this systematic scoping review aims to critically map and evaluate the traditional knowledge, phytochemistry, and preclinical experimental evidence regarding the anticancer potential of *H. indicus*, providing a comprehensive architecture to identify critical research gaps and guide future clinical development.

2. Materials and Methods

2.1 Protocol and Reporting Guidelines

This systematic scoping review was structured and conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines.

2.2 Objective

The primary objective of this review is to systematically map and evaluate the existing preclinical experimental evidence, encompassing *in vitro*, *ex vivo*, and *in silico* studies, regarding the anticancer potential of *Hemidesmus indicus*.

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2.3 Information Sources

A comprehensive literature search was conducted across major databases to identify relevant preclinical pharmacological studies.

2.4 Search Strategy

The search strategy utilised a combination of Medical Subject Headings (MeSH) and free-text terms related to *Hemidesmus indicus* and experimental oncology.

2.5 Eligibility Criteria

Studies were deemed eligible for inclusion if they represented primary experimental research (*in vitro*, *ex vivo*, or *in silico*) specifically investigating the anticancer, antileukaemic, or anti-angiogenic effects of *Hemidesmus indicus* plant extracts or their isolated phytocomplexes. The review included studies evaluating the plant's efficacy across various cancer models, such as breast cancer, colorectal cancer, promyelocytic leukaemia, and acute lymphoblastic leukaemia.

2.6 Study Selection Process

Following the removal of duplicates, the study selection process involved a screening of titles, abstracts, and full texts against the predefined eligibility criteria, ultimately resulting in the inclusion of seven principal preclinical studies for systematic synthesis.

2.7 Data Charting and Extraction

A standardised data charting form was developed to systematically extract relevant variables from the selected studies, which included the Author, Cancer Type, Experimental Model, Plant Part utilised, Extract formulation (e.g., methanolic, decoction, hydroalcoholic), Assays Performed, Molecular Targets, Outcomes, and Major Conclusions. (Table 2)

2.8 Data Synthesis

Data were synthesised qualitatively by mapping the reported preclinical outcomes to specific biological mechanisms and cancer hallmarks. The extracted data were categorised into functional domains, including intrinsic and extrinsic apoptosis, cell-cycle arrest (e.g., S-phase, G0/G1, G2/M checkpoints), intracellular calcium mobilisation, terminal cytodifferentiation, oxidative and endoplasmic reticulum (ER) stress, anti-angiogenesis, metastasis inhibition, and the induction of immunogenic cell death (ICD) via the mobilisation of damage-associated molecular patterns (DAMPs). Additional synthesis evaluated the genoprotective (chemopreventive) properties of the extracts alongside *in silico* receptor inhibition profiling.

2.9 Handling of Traditional Ayurvedic and Phytochemical Resources

To bridge traditional ethnopharmacology with modern molecular oncology, classical Ayurvedic texts and phytochemical databases were utilised strictly to provide contextual background and were purposefully excluded from the systematic evidence synthesis of experimental preclinical data. Specifically, traditional Ayurvedic resources were referenced to document the historical prescription of *Hemidesmus indicus* formulations for the treatment of neoplasms, *Raktavikara* (blood diseases), *Daha* (fevers or inflammation), and *Visha* (poisoning). Furthermore, the IMPPAT (Indian Medicinal Plants, Phytochemistry And Therapeutics) [5] database was utilised solely for contextual phytochemical mapping, identifying specific bioactive constituents and delineating their anatomical distribution across roots, stems, leaves, and flowers.

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2.10 Quality Appraisal of Included Studies

As this review follows a scoping methodology, a formal risk-of-bias or quality appraisal was not conducted, consistent with PRISMA-ScR guidance, which prioritises breadth of evidence mapping over methodological grading. However, basic indicators of study rigour, including sample replication, use of validated assay techniques, and consistency of reported molecular endpoints, were considered qualitatively during data charting to contextualise the strength of individual findings.

3. Results

3.1 Study Selection

The initial comprehensive literature search across the designated databases yielded a total of 68 potentially relevant records. Following the removal of 25 duplicate citations, the remaining 43 unique records were subjected to a rigorous primary screening of titles and abstracts to determine their preliminary relevance to the review objective. This primary screening phase resulted in the exclusion of 24 records that clearly did not meet the predefined inclusion parameters, leaving 19 full-text articles to be retrieved for a comprehensive eligibility assessment. During the full-text evaluation process, 12 studies were further excluded for specific reasons, including lack of relevant preclinical data, non-cancer disease focus, and insufficient characterisation of the phytocomplex. Ultimately, a total of seven principal preclinical studies successfully met all stringent eligibility criteria and were formally included in the final systematic evidence synthesis. The complete identification, screening, eligibility assessment, and inclusion process is visually delineated in Figure 1 (PRISMA-ScR Flow Diagram) in strict accordance with the PRISMA-ScR reporting guidelines.

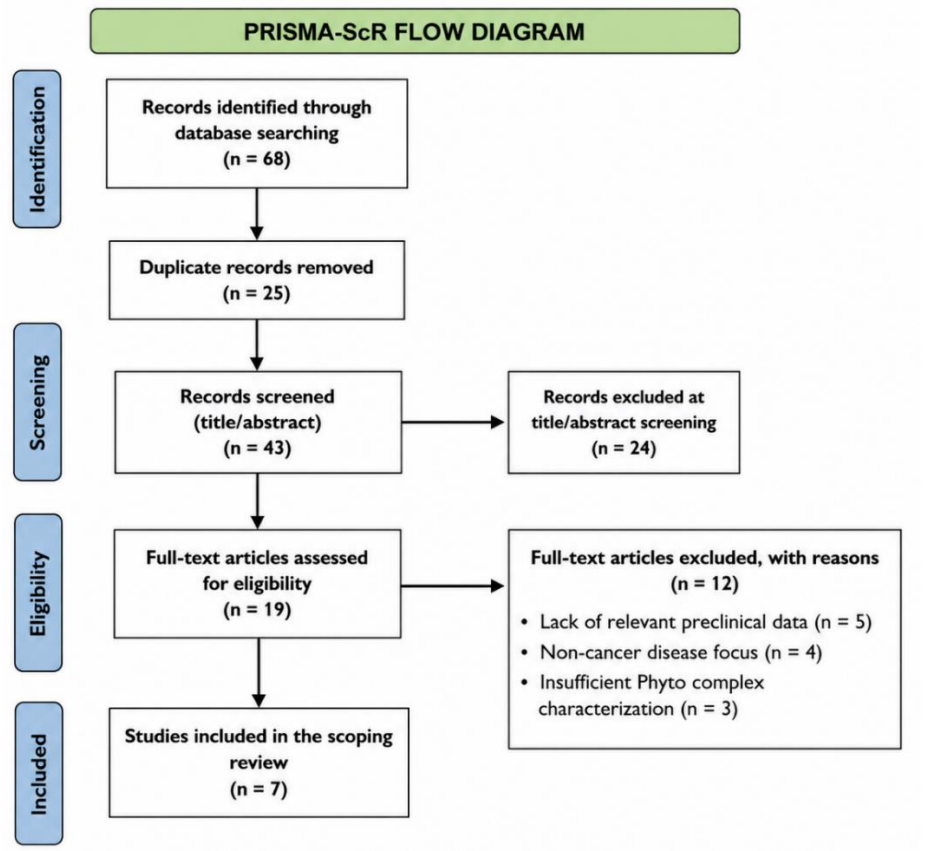


Figure 1. PRISMA-ScR Flow Diagram

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3.2 Phytochemical Landscape of *Hemidesmus indicus*

3.2.1. Root Phytocomplex

The roots of *Hemidesmus indicus* are the principal anatomical structures utilised in traditional Indian medicine and constitute the primary focus of modern preclinical oncological evaluation [5]. Extensive phytochemical screening using RP-HPLC-DAD has established that the root phytocomplex is heavily dominated by benzaldehydes and phenolic acids. The most abundant bioactive phytomarker is 2-hydroxy-4-methoxybenzaldehyde (MBALD), an aromatic volatile constituent that imparts a characteristic vanilla-like aroma to the roots and accounts for a significant portion of the total phytocomplex. Other principal constituents identified and quantified in the root decoctions and hydro-alcoholic extracts include 3-hydroxy-4-methoxybenzaldehyde, 4-hydroxybenzaldehyde, 2-hydroxy-4-methoxybenzoic acid, and vanillic acid [7]. Table 1 details the phytochemical component, part of the plant and its specific anticancer mechanism.

Table 1. Phytochemical Landscape of *Hemidesmus indicus*

Phytochemical Component	Plant Part(s)	Associated Cancer Type	Functional Role / Molecular Mechanism
2-Hydroxy-4-methoxybenzaldehyde (MBALD)	Root	Broad Spectrum (Colorectal, Breast, Leukaemia, Lung)	• Exhibits strong antioxidant/radical scavenging properties and acts as an anti-inflammatory by inhibiting nitric oxide (NO) production in macrophages. Exhibits weak direct antiproliferative activity alone, relying on phytocomplex synergy.
3-Hydroxy-4-methoxybenzaldehyde (3H4MB)	Root	Broad Spectrum (Colorectal, Breast, Leukaemia)	• Contributes to the antioxidant capacity of the extract and phytocomplex synergy. • Fails to induce isolated apoptosis but aids in overall extract efficacy.
2-Hydroxy-4-methoxybenzoic acid (2H4MBA)	Root	Broad Spectrum (Colorectal, Breast, Leukaemia)	• Functions primarily through free-radical scavenging (antioxidant) and NO inhibition. • Essential component of the synergistic matrix but weak as a standalone antiproliferative agent.
Rutin	Flower, Leaf	Breast Cancer (TNBC and HER2-positive)	• Identified via *in silico* virtual screening as a high-affinity ligand. • Computationally demonstrates potent inhibition of HER2, PARP1, PTK6, and c-Met protein receptors involved in breast cancer signal transduction.
Taraxasteryl acetate	Root	Breast Cancer (TNBC)	• Identified via *in silico* docking assays as a superior virtual hit. • Computationally inhibits CDK2 (blocking cell cycle), EGFR (epidermal growth factor receptor), and PARP2 (poly (ADP-ribose) polymerase).

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Vanillin / Vanillic acid	Root, Stem (Vanillin); Root (Vanillic acid)	Acute Lymphoblastic Leukaemia, Colon Adenocarcinoma	• Key secondary metabolites in the root extract. Contributes to the complex's ability to trigger both intrinsic/extrinsic apoptosis pathways and mitigate DNA damage (genoprotection).
Lupeol, Quercetin, & β-Sitosterol	Root, Stem (Lupeol, β-Sitosterol); Flower, Leaf, Root (Quercetin)	*General Phytocomplex Synergy*	• While not individually tested in the seven primary studies, these are prominent bioactive compounds identified across multiple plant parts. • They likely contribute to the synergistic multi-target efficacy (the "matrix effect") necessary for the plant's overall cytotoxicity and immune modulation.
Whole Extract Matrix (Decoction / Hydroalcoholic / Soxhlet)	Roots (predominantly), Whole Plant	Hallmarks: Apoptosis, Angiogenesis, ICD, Proliferation	• Contains the complete matrix required for multi-target activity. • Induces Immunogenic Cell Death (ICD) via ER stress (CRT, ATP, HMGB1 release), blocks VEGF/HIF-1α angiogenesis, and halts the cell cycle in S or G0/G1 phases.

3.2.2 Aerial Parts (Leaves, Flowers, Stems)

While modern analytical oncology has predominantly focused on the root, comprehensive phytochemical mapping of the aerial parts reveals a distinct and highly promising chemical fingerprint. The flowers and leaves of *H. indicus* are characterised by a profound concentration of high-affinity flavonoids, specifically rutin, quercetin, isoquercitrin, and hyperoside. Furthermore, the stems of the plant are distinguished by the presence of numerous alkaloids, including hemidescine, hemidine, heminine, emidine, and indicine. *In silico* virtual screening has demonstrated that flavonoids concentrated in the aerial parts, such as rutin, exhibit superior binding affinities to breast cancer target receptors, including HER2, PARP1, ERK2, and PTK6, compared to several FDA-approved oncological drugs. (Figure 2)



Figure 2. *Hemidesmus indicus (Sariva)* (A-Flower, B-Plant, C-Root) (Image Courtesy: Royal Botanic Gardens, Kew, Available at: powo.science.kew.org, Utilised under Creative Commons License.)

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3.3 Traditional Ayurvedic Knowledge vs. Modern Oncology

3.3.1 Raktavikara (Blood Diseases) and Antileukaemic Activity

In traditional Ayurvedic medicine, herbal preparations containing *Hemidesmus indicus* roots are extensively prescribed for the treatment of *Raktavikara* (hematologic or blood diseases) alongside direct applications for neoplasms (Example: *Sariva Kalpa, Sarivadyasava, Sarivadi Vati, Mahamanjishthadi Kashayam,* etc.) [4]. Modern preclinical oncology has successfully bridged this ethnopharmacological use by demonstrating the plant's potent antileukaemic activity across multiple experimental models. *In vitro* and *ex vivo* analyses reveal that root extracts exert profound cytotoxic and cytostatic effects against T-lymphoblastic leukaemia, promyelocytic leukaemia, and primary blasts isolated directly from patients with acute myeloid leukaemia (AML) [8]. Mechanistically, the extract halts unchecked leukaemic proliferation by inducing a G0/G1 or S-phase cell-cycle block and triggers apoptosis via mitochondrial depolarisation and intracellular calcium mobilisation. Furthermore, the phytocomplex is uniquely capable of overcoming the leukaemic differentiation block, forcing immortal, undifferentiated tumour blasts to undergo terminal cytodifferentiation into mature, functional granulocytes and macrophages, providing robust molecular validation for its traditional efficacy in blood disorders [5].

3.3.2 Daha (Fever/Inflammation) and Immunogenic Cell Death (ICD)

Traditional medical practitioners actively utilise *H. indicus* to alleviate *Daha* (burning sensation), *Jwara (*fevers and severe systemic inflammation) [4]. This traditional systemic anti-inflammatory application aligns intriguingly with modern preclinical evidence detailing the extract's ability to trigger immunogenic cell death (ICD) in solid tumours, effectively bridging inflammation modulation with tumour-specific immune responses [9]. In human colorectal cancer models, *H. indicus* induces lethal endoplasmic reticulum (PERK) stress and massive intracellular oxidative stress, forcing the dying tumour cells to mobilise specific damage-associated molecular patterns (DAMPs) [9]. This spatiotemporal cascade includes the early surface exposure of "eat me" signals like calreticulin and HSP70, followed by the secretion of ATP and the late-stage release of the pro-inflammatory mediator HMGB1. By releasing these factors, the dying cancer cells act as an "endogenous vaccine," which subsequently promotes the maturation of dendritic cells (evidenced by CD83 and CD86 up-regulation) and stimulates monocytes to release IL-6, thereby recruiting the host's adaptive immune system to target the malignancy [9].

3.3.3 Visha (Poisoning) and Genoprotection (Chemoprevention)

Ayurvedic texts classify the roots of *H. indicus* as a potent *Vishahara* (anti-poisoning) agent, heavily prescribed for neutralising snake bites, scorpion stings, and general toxic exposure [4]. In the context of modern oncology and pharmacology, this traditional anti-poisoning role translates directly to the plant's profound genoprotective and chemopreventive capabilities. Experimental models demonstrate that the extract actively protects healthy cellular DNA from severe mutagenic, clastogenic, and aneugenic "poisons"—including hydrogen peroxide (H_2O_2), doxorubicin, and etoposide. It significantly mitigates DNA double-strand breaks, objectively measured by a stark reduction in P-H2AX phosphorylation following toxic exposure [10]. The phytocomplex achieves this genoprotection through a dual mechanism: desmutagenic action, wherein it neutralises and chemically inactivates toxins in the extracellular space via strong antioxidant radical scavenging, and bioantimutagenic action, wherein it operates intracellularly to prevent the fixation of DNA damage and support cellular repair [10].

3.4 Preclinical Anticancer Mechanisms (*In Vitro* & *Ex Vivo*)

Table 2 presents a summary of the seven preclinical anticancer studies included in this review on phytochemistry and preclinical evidence in cancer research.

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Table 2. Summary of Preclinical Anticancer Studies

Author	Cancer Type	Extract	Assays Performed	Molecular Targets	Outcomes	Major Conclusions
Bansod et al.	Breast cancer.	Methanolic extract and 47 virtual ligands.	Virtual screening via Autodock Vina, SwissADME, and RP-HPLC.	Target receptors including CDK2, EGFR, ERK2, HER2, PARP1, PARP2, and PTK6.	Taraxasteryl acetate and Rutin showed superior binding affinities to breast cancer receptors compared to FDA-approved drugs.	Computational evidence supports the inhibitory activity of HI compounds against potential breast cancer drug targets.
Turrini et al.	Colorectal cancer.	Decoction.	APH and MUH viability assays, flow cytometry, intracellular ROS, extracellular ATP, and immunofluorescence.	ER stress (PERK), ROS, calreticulin, HSP70, ATP, HMGB1, and CD83/CD86 on DCs.	Induced ER and oxidative stress alongside ICD markers (ecto-CRT, ATP, HMGB1) and promoted DC maturation.	HI actively induces immunogenic cell death and has potential relevance in innovative cancer immunotherapy protocols.
Fimognari et al.	Leukaemia.	Decoction.	HPLC, cell cycle, Annexin V, caspase assays, JC-1, and Fluo-3 flow cytometry.	Mitochondrial transmembrane potential, Bax/Bcl-2, Ca2+ stores, Caspase-3, PARP, CDK2, Cyclin E, and p21.	Induced apoptosis via mitochondrial depolarization and intracellular Ca2+ rise, caused S-phase arrest, and enhanced the efficacy of chemotherapeutic drugs.	HI possesses potent antileukaemic properties mediated by the mitochondrial pathway and functions effectively as an adjunct to conventional chemotherapy.
Turrini et al.	Tumour angiogenesis (broadly supports tumour growth).	Decoction.	Flow cytometry, real-time PCR, cell migration/invasion, and capillary tube formation assays.	VEGF, HIF-1α, and VEGFR-2.	Inhibited proliferation, endothelial cell migration/invasion, and capillary tube formation, with differential inhibition of	Anti-angiogenic activity results from multiple interactions with the angiogenic cascade, making it a

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					VEGF and HIF-1α based on oxygen levels.	promising therapeutic strategy for tumours.
Ferruzzi et al.	Promyelocytic leukaemia.	Decoction.	NBT reducing activity, α-naphthyl acetate esterase activity, flow cytometry, and light/transmission electron microscopy.	G0/G1 cell cycle progression.	Caused cytotoxicity, G0/G1 cell-cycle block, and successfully induced terminal differentiation into mature granulocytes and macrophages.	Its ability to target multiple mechanisms to force undifferentiated tumour cells into differentiation or apoptosis makes it a promising candidate for leukaemia therapy.
Statti et al.	Multiple (colorectal, breast, lung, leukaemia, hepatocellular).	Decoction, hydroalcoholic extract, and isolated principal constituents.	Antiproliferative assays, DPPH, ABTS, and NO inhibition assays.	Cellular proliferation, free radicals, NO production, and DNA protection.	Decoction and hydroalcoholic extracts strongly inhibited proliferation in several cell lines and showed significant genoprotective potential, while isolated compounds alone had weak activity.	Contains potent antiproliferative, antioxidant, and genoprotective properties that rely heavily on the combined phytocomplex.
Turrini et al.	Acute lymphoblastic leukaemia and colon adenocarcinoma.	Hydro-alcoholic root extract followed by Soxhlet extraction.	RP-HPLC-DAD, flow cytometry, caspase 3/8 colorimetric assays, and P-H2AX genotoxicity analysis.	Caspase 3 and 8, S-phase cell cycle checkpoints, and DNA damage (P-H2AX).	Induced apoptosis via intrinsic and extrinsic pathways, caused S-phase block, and mitigated DNA damage induced by various mutagens.	HI extract is a dual-action botanical product that targets both early stages of cancer via chemoprevention and late stages via chemotherapeutic effects.

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3.4.1 Apoptosis and Intracellular Signalling

Hemidesmus indicus (L.) R. Br. triggers profound programmed cell death across diverse cancer lineages by activating both the intrinsic and extrinsic apoptotic cascades [8,10]. In T-lymphoblastic and acute myeloid leukaemia models, the extract disrupts the intrinsic mitochondrial pathway by causing a severe loss of mitochondrial transmembrane potential and stimulating the cytosolic release of cytochrome C [8]. This mitochondrial depolarisation is heavily driven by a significant increase in the Bax/Bcl-2 ratio, favouring pro-apoptotic signalling [8]. Concurrently, the phytocomplex has been shown to engage the extrinsic receptor pathway, objectively measured by the marked activation of Caspase-8 in lymphoblastic cells [10]. Both of these upstream pathways converge to activate Caspase-3, leading to the subsequent cleavage and inactivation of poly ADP-ribose polymerase (PARP), a crucial DNA-binding enzyme and universal reporter of the apoptotic execution phase [8,10]. Furthermore, this extract-induced apoptosis in leukaemia is mechanistically tied to a massive elevation of intracellular calcium, which is mobilised entirely from internal endoplasmic reticulum stores rather than via extracellular influx [8].

3.4.2 Cell-Cycle Arrest and Terminal Differentiation

In addition to inducing direct cytotoxicity, *H. indicus* profoundly halts unchecked cancer proliferation by enforcing cytostatic blocks at cell type-specific cycle checkpoints [5]. In acute lymphoblastic and T-lymphoblastic leukaemia cells, the extract induces a significant accumulation of cells in the S phase, effectively preventing DNA replication [8,10]. This S-phase delay is molecularly supported by a sharp down-regulation of CDK2 and the cell proliferation marker Ki67, alongside an increased expression of cyclin E and the CDK inhibitor p21. Conversely, in promyelocytic leukaemia cells (HL-60), the cell cycle is arrested earlier at the G0/G1 checkpoint, whereas in colorectal adenocarcinoma cells (DLD1), treatment provokes a cytostatic block at the G2/M phase [10,11]. Beyond simple cycle arrest, the extract demonstrates the unique pharmacological capacity to overcome the leukaemic differentiation block; it actively forces immortal, undifferentiated promyelocytic blasts to undergo terminal cytodifferentiation into mature, fully functional macrophages and granulocytes [11].

3.4.3 Anti-Angiogenesis and Metastasis Inhibition

H. indicus impairs the microvascular support networks critical for solid tumour survival and expansion by functioning as a potent anti-angiogenic and anti-metastatic agent [12,13]. The root extract directly inhibits the ability of human umbilical vein endothelial cells (HUVECs) to proliferate and organise into functional capillary tube branch points [12]. Mechanistically, this suppression is context-dependent: in normoxic environments, the extract actively downregulates the expression of vascular endothelial growth factor (VEGF), whereas under hypoxic conditions (which frequently characterise the core of aggressive tumours), it fundamentally inhibits hypoxia-inducible factor-1α (HIF-1α), leading to a subsequent cascade down-regulation of both VEGF and its receptor VEGFR-2. Additionally, the extract severely restricts early metastatic processes by inhibiting endothelial cell migration and invasion, a blockade that remains effective across both hypoxic and normoxic states [12].

3.4.4 Immunomodulation

A notable mechanism of *H. indicus* is its capacity to subvert tumour immune evasion by triggering immunogenic cell death (ICD), effectively transforming dying cancer cells into an "endogenous vaccine" [9]. In colorectal cancer models, the extract orchestrates this immunogenicity by inducing massive intracellular oxidative (ROS) stress and lethal endoplasmic reticulum stress that is strictly dependent on the activation of the PERK pathway [9]. This severe dual-stress forces the dying tumour cell to mobilise specific damage-associated molecular patterns (DAMPs) in a highly coordinated spatiotemporal sequence: it triggers the pre-apoptotic cell-surface exposure of the "eat me" signals Calreticulin (CRT) and HSP70, followed swiftly by the early apoptotic secretion of ATP (a "find me" signal), and concludes with the late-stage extracellular release of the pro-inflammatory mediator

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HMGB1. The successful release of these ICD factors directly bridges the innate and adaptive immune systems; exposure to these DAMPs promotes the terminal maturation of CD14-derived immature dendritic cells – evidenced by a marked up-regulation of the co-stimulatory molecules CD83, CD86, and CD80 – and stimulates primary monocytes to increase the release of the cytokine IL-6 [9].

Across the seven included studies, findings converge on a consistent theme: whole-extract preparations (decoction or hydroalcoholic) consistently outperform isolated constituents in bioactivity, a pattern reported broadly across other botanical systems as well, where crude extracts frequently exceed the efficacy of their purified single compounds [14,15]. This mirrors direct comparisons in unrelated phytocomplexes, such as lycopene and oregano extracts, where the whole matrix, but not the isolated marker molecule, triggered apoptosis in leukaemic and other cancer cell lines [16,17]. It also reflects wider evidence that standardising botanicals against a single marker compound does not reliably predict actual bioactivity [18]. However, the seven H. indicus studies vary considerably in experimental model complexity, ranging from established cell lines (HL-60, DLD-1) to patient-derived primary blasts, which limits direct comparability of potency across studies. Extract type also differs (decoction vs. hydroalcoholic vs. methanolic), and concentrations and exposure times are not standardised across studies, complicating cross-study efficacy comparisons. This heterogeneity is not unique to *H. indicus*; similar inconsistencies in extract standardisation and unpredictable herb-drug interactions have been documented for other botanicals under oncological co-treatment [19,20], underscoring the need for harmonised experimental protocols going forward.

3.5 Computational (*In Silico*) Evidence

Structure-based virtual screening evaluated the phytochemicals of *Hemidesmus indicus* against protein receptors implicated in breast cancer signal transduction. Two compounds – the triterpenoid Taraxasteryl acetate and the flavonoid Rutin – emerged as superior hits, showing strong binding affinities to key oncological targets. Taraxasteryl acetate inhibited Cyclin-dependent kinase 2 (CDK2), Epidermal Growth Factor Receptor (EGFR), and Poly [ADP-ribose] polymerase 2 (PARP2), with minimum binding energies of −11, −11, and −12.4 kcal/mol, respectively. It formed three hydrogen bonds within the EGFR active site, but complexed with CDK2 without forming any hydrogen bonds. Rutin bound HER2, PARP1, and PTK6 (breast tumour kinase) with binding energies of −10.8, −12.4, and −10.4 kcal/mol, respectively, forming four hydrogen bonds with both HER2 and PARP1, and up to five with PTK6. Supplementary analysis also identified Rutin as an emerging c-Met inhibitor, suggesting a possible therapeutic avenue for aggressive, late-stage triple-negative breast cancer (TNBC). In a comparative computational scenario, both Taraxasteryl acetate and Rutin showed binding affinities across all six receptors relative to conventional FDA-approved oncological drugs and analogues. This supports the rationale for developing these *H. indicus* phytochemicals as targeted templates for future breast cancer drug design [13].

3.6 Synergies, Drug Interactions, and Toxicity

3.6.1 Conventional Chemotherapy Synergies

In the preclinical evaluation of combinational therapies, *Hemidesmus indicus* has demonstrated significant potential to enhance the therapeutic efficacy of conventional chemotherapeutic agents. When combined with the purine analogue 6-thioguanine or the pyrimidine analogue cytarabine, the root extract exerted a highly synergistic pro-apoptotic effect against leukaemic cells, yielding favourable combination indices (CI) of 0.60 and 0.38, respectively [8]. Additionally, it demonstrated a clear additive apoptotic effect when co-administered with the antifolate methotrexate, actively sensitising normally resistant lymphoblastic models to the drug [8]. However, the complex nature of the botanical matrix dictates that predictable drug interactions cannot be universally assumed. For instance, the extract was found to unexpectedly potentiate the genotoxicity of camptothecin rather than mitigating it, an interaction likely stemming from components in the plant matrix acting as competing topoisomerase I inhibitors [10].

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3.6.2 Toxicity and Safety Profile

The promising therapeutic index of *H. indicus* is heavily supported by a favourable preclinical safety profile characterised by selective cytotoxicity. While the extract successfully eradicates diverse, aggressive cancer lineages, it actively spares normal human peripheral blood mononuclear cells (PBMCs) [9]. Specifically, concentrations that induce roughly 50% lethality in colorectal adenocarcinoma cells do not increase the apoptotic or necrotic cell fractions in healthy PBMCs, indicating a targeted capability to exploit tumour-specific vulnerabilities without widespread systemic destruction [9]. Furthermore, the phytocomplex provides a profound genoprotective (chemopreventive) effect on normal cells, actively shielding healthy DNA from oxidative and chemical mutagens [10]. Supporting these *in vitro* cellular models, preliminary *in vivo* acute toxicity evaluations in Swiss albino mice reported no lethality or conspicuous behavioural alterations following the administration of root powder suspensions. In these mammalian models, the calculated LD50 (lethal dose for 50% of the population) for hepatic and renal toxicity is estimated to be at least 130 times higher than the active *in vitro* concentrations used to trigger immunogenic cell death [9]. Multi-Target Mechanisms of *H. indicus* in Cancer Cells showing apoptosis, cell-cycle arrest, anti-angiogenesis, and ICD induction (DAMP release) are shown in Figure 3.

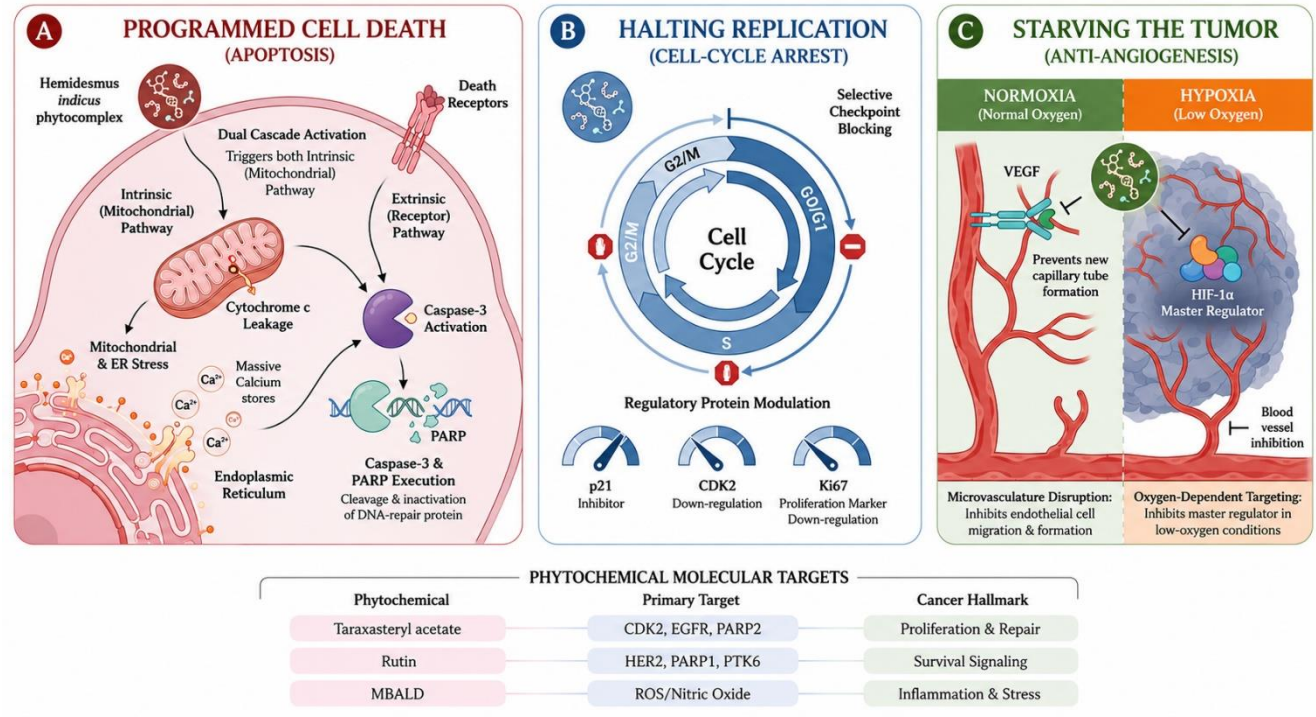


Figure 3. Multi-Target Mechanisms of *H. indicus* in Cancer Cells: A visual pathway map showing apoptosis, cell-cycle arrest, anti-angiogenesis, and ICD induction (DAMP release)

4. Discussion

4.1 Summary of Evidence

The preclinical evidence synthesised in this review suggests that *Hemidesmus indicus* (L.) R. Br. operates as a potent, multi-target botanical drug in experimental oncology. Unlike conventional mono-targeted therapies, which frequently induce adaptive chemoresistance due to the redundant signalling networks inherent to tumours, the complex phytochemical matrix of *H. indicus* simultaneously disrupts multiple critical nodes within the cancer cellular network [8]. Its broad-spectrum anticancer efficacy is driven by a profound synergy among its constituents,

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which interact with numerous molecular receptors to orchestrate intrinsic and extrinsic apoptosis, force specific cell-cycle phase blocks, and induce terminal cytodifferentiation in undifferentiated leukaemic blasts [11]. Furthermore, this multi-target capacity extends beyond direct cytotoxicity into the tumour microenvironment; the extract actively restricts metastatic spread and tumour angiogenesis by down-regulating VEGF and HIF-1α [12], while simultaneously triggering immunogenic cell death (ICD) by exposing damage-associated molecular patterns (DAMPs) that act as an "endogenous vaccine" to alert the host immune system [9].

4.2 Critical Research Gaps

Despite the highly promising molecular validation bridging traditional Ayurvedic knowledge with modern pharmacology, the translation of *H. indicus* into clinical oncology is severely restricted by several critical research gaps. Primarily, the current body of evidence remains strictly preclinical, heavily confined to isolated *in vitro* cell cultures and *in silico* computational simulations [13]. There is a pronounced absence of rigorous *in vivo* animal models and human clinical trials, which are necessary to confirm actual systemic therapeutic efficacy, pharmacokinetic profiles, and bioaccessibility. Additionally, the standardisation of the botanical phytocomplex poses a significant pharmacological challenge. Because the anticancer and genoprotective properties rely heavily on the "matrix effect" of the entire crude extract rather than isolated constituent compounds, variations in raw material quality, complex drug-drug interactions with conventional chemotherapies, and the unpredictable release of key components from the plant matrix remain poorly mapped and require comprehensive profiling [10,11].

A further limitation relates to the literature base itself. The search was restricted to specific electronic databases and may not capture regional or non-English language publications on Ayurvedic pharmacology, potentially introducing language and database selection bias. Additionally, as with most preclinical botanical research, studies reporting positive or significant anticancer activity are more likely to be published than those reporting null or inconclusive results, raising the possibility of publication bias that this review cannot fully account for given its qualitative synthesis design.[21]

4.3 Future Prospects

Moving forward, the systematic evaluation of *H. indicus* must expand beyond its traditionally utilised roots to explore the untapped potential of its aerial parts. Phytochemical mapping reveals that while root extracts are dominated by benzaldehydes, the leaves and flowers of the plant are highly concentrated in potent, high-affinity flavonoids, notably rutin, quercetin, isoquercitrin, and hyperoside. Computational *in silico* virtual screening specifically demonstrates that these aerial flavonoids, such as rutin, exhibit superior binding affinities to critical breast cancer receptors—including HER2, PARP1, c-Met, and PTK6 [12,13]. Therefore, addressing the standardisation challenges of the complex plant matrix, investigating the synergistic potential of aerial phytochemicals, and actively transitioning these robust *in vitro* and *in silico* findings into rigorous *in vivo* models and human clinical trials will be essential to fully realise the promise of *H. indicus* as a viable botanical drug in clinical oncology.[22,23]

Concretely, future studies should prioritise standardised extraction and quality-control protocols (e.g., fixed solvent ratios and phytomarker quantification benchmarks) to ensure batch-to-batch reproducibility, alongside formal pharmacokinetic studies to establish bioavailability and systemic exposure. Comprehensive toxicity evaluation, including repeated-dose and organ-specific studies beyond the acute LD50 data currently available, will also be necessary. Finally, well-controlled animal efficacy studies using relevant tumour models are needed as a direct bridge before any consideration of early-phase clinical trials.

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5. Conclusion

This systematic scoping review indicates that *Sariva*, *Hemidesmus indicus* (L.) R. Br. is a promising multi-target botanical drug candidate for oncology, molecularly validating its traditional *Ayurvedic* use in blood-related disorders, inflammation, and neoplasms. However, the evidence base remains strictly preclinical, and clinical translation will require standardisation of the phytocomplex, in vivo validation, and systematic drug-interaction profiling. Future research should prioritise the untapped aerial parts, whose flavonoid-rich profile may offer therapeutic potential beyond the traditionally used roots. On clinical validation, *H. indicus* could emerge as a stand-alone multi-target botanical drug or a synergistic chemotherapy adjuvant.

Abbreviations:

FDA: Food and Drug Administration, MBALD: 2-hydroxy-4-methoxybenzaldehyde, 3H4MB: 3-hydroxy-4-methoxybenzaldehyde, 2H4MBA: 2-hydroxy-4-methoxybenzoic acid, IMPPAT: Indian Medicinal Plants, Phytochemistry And Therapeutics, ICD: Immunogenic Cell Death, DAMP(s): Damage-Associated Molecular Pattern(s), ER: Endoplasmic Reticulum, PERK: Protein kinase RNA-like Endoplasmic Reticulum Kinase, ROS: Reactive Oxygen Species, CRT: Calreticulin, ATP: Adenosine Triphosphate, HMGB1: High Mobility Group Box 1, DC(s): Dendritic Cell(s), CD83/CD86/CD80/CD14: Cluster of Differentiation 83/86/80/14, IL-6: Interleukin-6, PBMCs: Peripheral Blood Mononuclear Cells, RP-HPLC-DAD: Reverse Phase-High Performance Liquid Chromatography-Diode Array Detector, TNBC: Triple-Negative Breast Cancer, HER2: Human Epidermal growth factor Receptor 2, PARP1/PARP2: Poly [ADP-ribose] Polymerase 1/2, PTK6: Protein Tyrosine Kinase 6, c-Met: MET proto-oncogene (Mesenchymal-Epithelial Transition factor), CDK2: Cyclin-Dependent Kinase 2, EGFR: Epidermal Growth Factor Receptor, VEGF: Vascular Endothelial Growth Factor, VEGFR-2: Vascular Endothelial Growth Factor Receptor 2, HIF-1α: Hypoxia-Inducible Factor-1 alpha, HUVECs: Human Umbilical Vein Endothelial Cells, AML: Acute Myeloid Leukaemia, NO: Nitric Oxide, DPPH: 2,2-Diphenyl-1-picrylhydrazyl, ABTS: 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), NBT: Nitroblue Tetrazolium, Bax/Bcl-2: BCL2-Associated X protein / B-cell Lymphoma 2, γ-H2AX (P-H2AX): Phosphorylated H2A histone family member X, LD50: Lethal Dose, 50 percent, CI: Combination Index.

Declarations

Data Availability

The data supporting the findings of this study were derived from publicly available published literature and publicly accessible databases, including the Indian Medicinal Plants, Phytochemistry and Therapeutics (IMPPAT) database and classical Ayurvedic literature. All relevant data generated through literature extraction and synthesis are included within the manuscript.

Informed Consent Statement

Not applicable.

Ethics Statement/Ethical Approvals

Not applicable. This study is a systematic scoping review based exclusively on published literature and publicly available databases and did not involve human participants, animals, or any primary experimental investigations requiring institutional ethical approval.

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NA

Conflict of Interest

The authors declare no conflict of interest.

Authors' Contribution

VS: Conceptualisation, methodology, literature search, data curation, data synthesis. **PS:** Conceptualisation, methodology, literature search, writing—original draft preparation. **SST:** Data curation, Data synthesis, writing—review and editing. **SB:** Writing—review and editing. **PPH:** Writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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