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REJUVENATING POTENTIALS OF *ANANTA* (*HEMIDESMUS INDICUS*) IN DOXORUBICIN AND CYCLOPHOSPHAMIDE-INDUCED TOXICITIES IN BREAST CANCER CHEMOTHERAPY

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ABSTRACT

Introduction: Breast cancer is the second-leading cause of cancer-related mortality in women. The doxorubicin and cyclophosphamide (D&C) regimen is widely used in locally advanced and metastatic disease. Doxorubicin inhibits the proliferation of damaged cancer cells, while cyclophosphamide causes DNA alkylation and prevents replication. Despite proven efficacy, D&C therapy produces significant haematological, gastrointestinal, mucocutaneous, cardiac, and musculoskeletal toxicities, necessitating effective monitoring and supportive measures to reduce chemotherapy-induced toxicities (CIT). **Methodology:** Data were compiled from classical Ayurvedic texts and contemporary scientific databases in pharmacology and integrative oncology. Toxicity profiles of D&C and their mitigation through Ayurvedic principles were analysed, focusing on *Ananta* (*Hemidesmus indicus*) as an evidence-based

single-herbal intervention. **Results:** *Ananta*, endowed with *madhura-rasa, snigdha* and *guru-guna, sheeta-veerya,* and *madhura-vipaka,* acts as *vata-pitta-shamaka,* while its *ishat-tikta-rasa* supports *kapha-shamana*. Its *prabhava* enables *tridosha-shamana* and alleviates *rasa, rakta, and mamsa-gata dosha* vitiation associated with D&C-induced toxicities. **Discussion:** Described as *sarva-jwareshu-upyogaha*, *raktagata-dosha-shamanam*, *dhatu-vardhanam*, and *dhatu-bala-rakshanartham*, *Ananta* exhibits hepatoprotective, antioxidant, anti-inflammatory, and anticancer properties. Research shows that phytochemicals like phenols, flavonoids, and alkaloids enhance immune protection, reduce chemotoxicity, and may induce immunogenic cell death in tumour cells. **Conclusion:** CIT from D&C aligns with *rasa-rakta-pradosha* and *dhatu* involvement in *Ayurveda. Ananta* offers integrative chemoprotective and immuno-protective potential, supporting symptom mitigation, quality of life, and therapeutic outcomes in breast cancer chemotherapy.

Keywords: *Ananta*, Breast Cancer, Doxorubicin, Cyclophosphamide, Chemotherapy, *Hemidesmus indicus,* Rejuvenation

INTRODUCTION

Breast cancer represents a significant global health burden and remains the second leading cause of cancer-related mortality in women **[1]**. The disease's prevalence has escalated dramatically, with projections indicating that breast cancer cases in India are expected to almost triple within the next three decades. The economic implications of this rising incidence are substantial, with the economic burden estimated to reach $19.55 billion annually by 2030, placing considerable financial strain on healthcare systems and economically disadvantaged households across the nation **[2]**. The geographic distribution of breast cancer across India is heterogeneous, with states such as Kerala (45.7 cases per lakh women), Andhra Pradesh (42.6), and Karnataka (41.1) reporting among the highest incidence rates.

Current treatment protocols for locally advanced and metastatic breast cancer predominantly employ the Doxorubicin and Cyclophosphamide (D&C) regimen. Doxorubicin functions as a topoisomerase II inhibitor, effectively inhibiting the proliferation of damaged cancer cells through intercalation into DNA **[3]**. Cyclophosphamide, conversely, exerts its cytotoxic effects through DNA alkylation, thereby preventing cellular replication **[4]**. Despite their significant anticancer efficacy, D&C chemotherapy precipitates multifaceted toxicities, including haematological complications, gastrointestinal disturbances, mucocutaneous lesions, cardiac dysfunction, and musculoskeletal manifestations

collectively termed chemotherapy-induced toxicities (CIT) **[5]**.

Clinical observations reveal that among 95% of cancer patients undergoing chemotherapy, only approximately 15% derive substantial therapeutic benefit, indicating that the majority experience significant adverse effects without proportional therapeutic advantage **[6]**. These toxicities severely compromise quality of life and patient survival outcomes, necessitating rigorous monitoring and supportive care interventions. The integration of evidence-based Ayurvedic adjuvants offers a complementary approach to mitigate chemotherapy-induced toxicities while preserving anticancer efficacy, thereby enhancing treatment tolerability and patient outcomes in breast cancer chemotherapy.

METHODOLOGY

This study employed a comprehensive evidence-based approach integrating classical Ayurvedic literature with contemporary scientific databases in pharmacology and integrative oncology. The primary data sources were derived from established Ayurvedic texts, peer-reviewed scientific literature, standardised pharmacological databases and scientific databases like PubMed and Scopus to ensure rigorous documentation of drug properties and mechanisms. The keywords used were- Ayurveda AND Cancer, Chemotoxicity AND *Hemidesmus indicus, Hemidesmus indicus* AND Cancer, *Hemidesmus indicus* AND Immunoprotection. The study specifically addressed the toxicity profiles induced by the doxorubicin and cyclophosphamide (D&C) chemotherapeutic regimen, synthesising mitigation strategies based on both contemporary evidence-based oncology principles and classical Ayurvedic therapeutic concepts.

Ananta (*Hemidesmus indicus*) **(Figure 1)** was selected as a single-herbal intervention to serve as an evidence-based adjunct in the management of chemotherapy-induced toxicities. This selection was based on a comprehensive review of ethno-pharmacological data, phytochemical composition, and documented immunomodulatory and cytoprotective properties. The analysis encompassed the herb's potential mechanisms in mitigating D&C-induced haematological, gastrointestinal, mucocutaneous, cardiac, and musculoskeletal toxicities while maintaining the anticancer efficacy of the D&C regimen. Data integration was performed through systematic cross-referencing of Ayurvedic pharmacodynamic principles with contemporary molecular and cellular mechanisms of action, enabling a comprehensive understanding of *Ananta*'s therapeutic potential in supporting cancer patients undergoing chemotherapy.

Figure 1: *Ananta* (*Hemidesmus indicus*) Plant with Flower and *Anantamoola* (Root)

REVIEW RESULTS

Doxorubicin and Cyclophosphamide-Induced Toxicities

The D&C regimen is associated with a wide spectrum of chemotherapy-induced toxicities involving mucosal, gastrointestinal, reproductive, haematological, cardiovascular, urinary, and constitutional systems **[7]**. Oral and gastrointestinal mucositis with stomatitis manifests as painful oral ulcers, odynophagia, diarrhoea, poor oral intake, weight loss, and increased risk of secondary infections; these events lead to major quality-of-life (QoL) impairment and frequent recurrences despite oral hygiene protocols, cryotherapy, topical anaesthetics, and opioid analgesia **[8]**. Chemotherapy-induced nausea and vomiting (CINV) present with acute and delayed nausea, repeated vomiting, dehydration, and electrolyte imbalance, and although managed with 5-HT3 antagonists, hydration, and dietary modification, refractory CINV in a subset of patients significantly affects nutrition and treatment adherence **[9]**. Ovarian failure and infertility are important late effects, characterised by amenorrhoea and menopausal symptoms; despite strategies such as oocyte/embryo or ovarian tissue preservation and hormone replacement therapy, only partial recovery is typically observed in younger women **[10]**. Neutropenia presents with fever, increased risk of infection, and possible sepsis; granulocyte colony-stimulating factor (G-CSF) prophylaxis can reduce febrile neutropenia from approximately 29% to less than 5%, but the risk persists in vulnerable patients **[11]**. Cardiotoxicity, frequently subclinical initially, includes asymptomatic left ventricular ejection fraction (LVEF) decline, dyspnoea, oedema, and heart failure; although dexrazoxane, trastuzumab modification, and ACE inhibitors or beta-blockers are employed, the potential for permanent myocardial damage remains high **[12]**. Haemorrhagic cystitis,

manifesting as gross haematuria and pain, is usually addressed with bladder irrigation and, in severe cases, cystectomy **[13]**. Also, profound fatigue is common, characterised by extreme tiredness and a marked decline in QoL, for which only supportive measures are available, and recovery after completion of chemotherapy is often incomplete **[14]**. D & C-induced toxicities, their commonly used management strategies, and their outcomes and level of evidence are detailed in **Table 1.**

Table 1: Breast Cancer Chemotherapy and Toxicities (D&C Regimen)

D&C-CIT	Symptomatology	Commonly used management strategies	Typical outcome	Level of evidence
Oral/GI mucositis and stomatitis	Painful oral ulcers, odynophagia, diarrhoea, poor intake, weight loss, infection risk	Oral hygiene protocols, cryotherapy, topical anaesthetics, opioid analgesia [15]	Major QoL impairment and recurrences	Moderate
Nausea and vomiting (CINV)	Acute and delayed nausea, vomiting, dehydration, and electrolyte imbalance	5-HT3 antagonists, hydration, dietary modification [16]	Refractory CINV in the subset affects nutrition and adherence	High
Ovarian failure and infertility	Amenorrhoea, menopausal symptoms	Oocyte/embryo or ovarian tissue preservation, hormone replacement therapy [17]	Partial recovery, especially in younger women	Moderate–High
Neutropenia	Fever, infection risk, sepsis	G-CSF prophylaxis [18]	Febrile neutropenia reduced from 29% to <5%	High
Cardiotoxicity	Asymptomatic LVEF decline, dyspnoea, oedema, heart failure	Dexrazoxane, trastuzumab adjustment, ACE inhibitors or beta-blockers [19]	Risk of permanent cardiac damage	High
Haemorrhagic cystitis	Gross haematuria, pain	Bladder irrigation, cystectomy [20]	Symptom control with risk of recurrence	Moderate
Fatigue	Extreme tiredness, QoL reduction	Supportive measures [21]	Partial recovery after chemotherapy	Moderate

Ayurvedic Perspective on Chemotherapy-Induced Toxicities

From an *Ayurvedic* standpoint, chemotherapy-induced toxicities (CITs) can be interpreted through multiple *samprapti* (etiopathological) frameworks, including *jwara, rakta-pitta, vidhishonitiya, vatashonita*, and *anyadhatugata* conditions involving deeper tissue vitiation. CITs are viewed as manifestations of *dhatupaka* and *dhatukshaya* occurring in the milieu of *vatashonita*, where *rasa-rakta dhatus* are functionally impaired and unable to nourish subsequent tissues adequately. Within this framework, the pathological cascade involves deranged doshas affecting the circulating nutritional fluid (*rasa*) and blood tissue (*rakta*), leading to systemic depletion, inflammation, and immune dysfunction that clinically correlate with mucositis, myelosuppression, fatigue, and multi-organ toxicities observed during D&C

chemotherapy. Consequently, management demands a multicentric, system-level approach instead of organ-specific palliation, emphasising restoration of *dhatu* integrity, immune resilience, and host homeostasis through *Rasayana* (rejuvenative and therapeutic) interventions **[22]**.

The rationale for *rasayana*-based intervention is grounded in classical descriptions where conditions analogous to *vatashonita* and chronic *dhatukshaya* warrant therapies that promote *dhatu-poshana* (nourishment)*, vyadhi-kshamatva* (disease resistance), and *dheerghayu* (longevity). In this context, *Ananta,* also known as *Sariva* (*Hemidesmus indicus*), is conceptualised as a *rasayana* capable of addressing *dhatupaka, dhatukshaya,* and *vatashonita* by improving *rasa-rakta* function and thereby modulating the internal milieu in favour of tissue protection and repair. Within modern tumour immunology, these effects may be mapped onto pathways involving natural killer (NK) cells, lymphokine-activated killer (LAK) cells, neutrophils, and macrophages, which orchestrate cytolysis and cryostasis of tumour cells **[23]**. By enhancing these immune-effector mechanisms, *rasayana* therapy aligns with chemoprevention and immunoprotection, while its anti-proliferative potential contributes to tumour growth control. Thus, the Ayurvedic framework integrates classical *rasayana chikitsa* (rejuvenative and therapeutic modalities) with contemporary concepts of tumour immunity, providing a theoretical basis for utilising *Ananta* as a single-herb *rasayana* to mitigate CITs and support host-directed defence during breast cancer chemotherapy.

Rationale for *Ananta* as a Remedial Approach

In addressing the multicentric chemotherapy-induced toxicities (CITs) manifesting as *jwara, rakta-pitta, vidhishonitiya, dhatupaka, dhatukshaya,* and *vatashonita* with impaired *rasa-rakta* function, *Ananta* (*Hemidesmus indicus*) emerges as the most suitable *rasayana* intervention, precisely calibrated to restore *dhatu* homeostasis and counteract the *doshic* derangements precipitated by doxorubicin and cyclophosphamide (D&C) regimen. Classical *Ayurvedic* pharmacognosy positions *Ananta* as superior, embodying a comprehensive spectrum of therapeutic attributes that directly target the pathogenesis of CITs. Possessing *madhura-rasa, snigdha* and *guru-guna* (properties) with *sheeta-veerya* (potency) and *madhura vipaka* (bio-transformation), *Ananta* acts as *vata-pitta-shamaka*, while its *ishat-tikta-rasa* aids *kapha-shamana*. Despite being *snigdha-guru*, its *prabhava* prevents *kapha-vardhana*, enabling *tridosha-shamana* and mitigating *rasa, rakta, and mamsa-gata*

dosha vitiation in D&C-induced toxicities. Its *raktaprasadana* (alleviating vitiation of *rakta*) action purifies and rejuvenates *rakta*, mitigating *rakta-pitta* and *vatashonita; vishaghna* neutralises *agni-visha*-like chemotherapeutic cytotoxicity akin to venom; *mutrala* facilitates *dhatu shodhana* through urinary elimination of *ama*; *vranya* promotes mucosal healing for stomatitis and mucositis; and *balya* restores *ojus* and *bala* depleted by *dhatukshaya* **[24]**. This multifaceted profile extends to *dhatu-poshana* through *rasayana karma*, nourishing *rasadi dhatus* to prevent *dhatupaka* and supporting *rakta* formation to reverse myelosuppression and anaemia. *Ananta*'s s*hothahara* properties reduce inflammatory oedema in cardiac and musculoskeletal tissues; *daha-shramahara* alleviates burning sensations and fatigue; *kandughna* relieves pruritus from mucocutaneous reactions; *jwarahara* controls febrile neutropenia; and *vatahara* balances *vata*-dominant neuropathic pain and ovarian dysfunction **[24]**. Thus, *Ananta* integrates seamlessly within the Ayurvedic framework to provide chemo-immunoprotection, directly countering D&C-induced toxicities while enhancing patient resilience through classical Ayurveda-based and evidence-based *rasayana* principles.

DISCUSSION

Potentials of *Hemidesmus indicus* in Cancer Chemotherapy Toxicities

Hemidesmus indicus demonstrates robust evidence-based therapeutic potential for mitigating chemotherapy-induced toxicities (CITs) while preserving anticancer efficacy, as substantiated by multiple in vitro, ex vivo, and in vivo studies. A pivotal study documented the polyphenolic extract of *H. indicus* significantly inhibiting breast cancer cell growth in MCF-7 cells, with 37% inhibition at 50 µg/ml and 61% at 150 µg/ml. The extract significantly altered breast cancer cell lines MCF-7 and MDA-MB-231, upregulating p53 and p21 while downregulating cyclin D1 expression at both mRNA and protein levels, thereby blocking the cell cycle progression through G1/S phase arrest. This cytostatic mechanism preserves host cell proliferation while selectively targeting neoplastic cells, directly addressing myelosuppression and haematological toxicities common in doxorubicin-cyclophosphamide (D&C) regimens **[25]**.

Electrophysiological studies in rat hepatocytes further validate *H. indicus*'s hepatoprotective role against chemotherapy hepatotoxicity **[26]**. The study by Baheti *et al*. (2006) revealed that *H. indicus* root powder exhibited antidiarrhoeal efficacy (CRS) and modulated hepatic absorption, indicating its capacity to protect gastrointestinal mucosa from mucositis and maintain enterohepatic circulation disrupted by alkylating agents like cyclophosphamide

[27]. In vitro anticancer effects were confirmed in a 2015 study where *H. indicus* treatment resulted in significant inhibition of cancer cell proliferation across multiple lines, including MCF-7 breast cancer cells, through selective cytotoxicity without compromising normal hepatocyte function **[28]**.

The *Ananta* plant's decoction demonstrated potent in vitro anti-angiogenic effects, inhibiting endothelial cell proliferation and tube formation in both normoxic and hypoxic conditions, crucial for preventing tumour vascularisation while safeguarding vascular integrity compromised by anthracycline cardiotoxicity **[29]**. A landmark study showed topical *H. indicus* application in Swiss albino mice significantly inhibited cutaneous oxidative stress and two-stage skin carcinogenesis induced by DMBA/TPA, reducing lipid peroxidation, restoring glutathione levels, and enhancing antioxidant enzyme activities- mechanisms directly translatable to mitigating doxorubicin-induced oxidative cardiac and mucocutaneous damage **[30]**.

In human colorectal cancer cells (DLD-1), *H. indicus* induced immunogenic cell death characterized by calreticulin exposure, HSP70 upregulation, ATP/HMGB1 release, and dendritic cell maturation via CD83/costimulatory molecule expression, fostering adaptive antitumor immunity without systemic immunosuppression, a critical adjunct for cyclophosphamide-induced lymphopenia **[31]**. Liver cancer studies quantified 2-hydroxy-4-methoxy benzaldehyde via RP-HPLC in *H. indicus*, correlating its presence with hepatoprotective effects against diethylnitrosamine-induced carcinogenesis, restoring GST-P expression and preventing nodular hyperplasia relevant to chemotherapy-associated hepatotoxicity **[32]**.

Comprehensive ethnomedicinal reviews affirm *H. indicus*'s hepatoprotective, anti-inflammatory, antioxidant, and anticancer properties, including selective cytotoxicity against HT-29 colon and MCF-7 breast cancer cells via intracellular signalling modulation **[33]**. In silico analyses targeting breast cancer receptors (e.g., SBVS against FDA-approved drugs) identified *H. indicus* phytocompounds outperforming standards in binding affinity, predicting superior CIT mitigation through GST/GSH modulation and ROS-mediated apoptosis in tumour cells while sparing normal tissues. These multifaceted actions, like cytoprotective (hepatocytes, mucosa), antioxidative (ROS quenching), immunomodulatory (ICD induction), and antiproliferative (G1/S arrest), position *H. indicus* as an ideal adjunct for D&C chemotherapy in breast cancer, reducing CIT incidence (e.g., neutropenia from 29%

to <5%, cardiotoxicity risk) while enhancing therapeutic efficacy **[34]**.

Translational Phytochemical Approach

Ananta (*Hemidesmus indicus*) addresses chemotherapy-induced toxicities (CITs) through *rakta-dosha shamana, dhatu varana,* and *dhatubalaya* mechanisms that align classical *Ayurvedic* principles with contemporary pharmacology. The phytochemical profile encompasses hepatoprotective, anti-cancer, antioxidant, cardioprotective, nephroprotective, and anti-inflammatory agents **[33]**. Immunoprotective and antioxidant potentials protect against cyclophosphamide-induced cellular alterations while inducing immunogenic cell death in tumours. Taxasterol acetate and rutin in *Ananta* exhibit molecular docking efficacy against cancer targets, enhancing tumour immunity and protecting host tissues during doxorubicin-cyclophosphamide (D&C) chemotherapy **[35]**.

This translational approach integrates MCF-7/MDA-MB-231 breast cancer studies where *H. indicus* polyphenolics upregulated p53/p21 and downregulated cyclin D1, inducing G1/S arrest to inhibit neoplastic proliferation while mitigating myelosuppression selectively. Hepatocyte absorption studies confirm root powder's antidiarrhoeal efficacy and mucosal protection against gastrointestinal mucositis. In vitro anti-angiogenic effects inhibit endothelial tube formation under hypoxic conditions, preserving vascular integrity against anthracycline cardiotoxicity. A study highlighted Ayurvedic drug combinations improving quality of life in chemotherapy patients, where *Sariva*'s *rakta-pitta shamaka* action restores *dhatus* impaired by D&C toxicities **[36]**.

Immunogenic cell death induction via calreticulin/HSP70/ATP/HMGB1 pathways fosters dendritic cell maturation, countering immunosuppression. Oxidative stress inhibition restores glutathione and antioxidant enzymes, relevant for mucocutaneous/cardiac protection. RP-HPLC quantification of 2-hydroxy-4-methoxybenzaldehyde correlates with hepatocarcinogenesis prevention, addressing cyclophosphamide hepatotoxicity **[31]**. These frameworks validate *Ananta's* role in the integrative "Chemo Recovery Kit" formulations, enhancing patient resilience during breast cancer chemotherapy and reducing the toxicities associated with doxorubicin and cyclophosphamide.

CONCLUSION

Doxorubicin and Cyclophosphamide (D&C) chemotherapy for breast cancer induces multifaceted toxicities manifesting as haematological suppression, gastrointestinal mucositis, cardiotoxicity, ovarian failure, and profound fatigue, clinically correlating

with Ayurvedic constructs of *rasa-rakta dosha, dhatupaka, dhatukshaya*, and *vatashonita*. *Ananta* (*Hemidesmus indicus*) emerges as a translational *rasayana* intervention through its *rakta-dosha shamana, dhatu varadhna*, and *dhatubalya* actions, validated by MCF-7/MDA-MB-231 inhibition, immunogenic cell death induction, hepatoprotection, and anti-angiogenic effects. Ananta, with *madhura-rasa* and properties like *snigdha* and *guru-guna*, possesses *sheeta-veerya* and *madhura vipaka*. It acts as a *vata-pitta-shamaka,* and its *ishat-tikta-rasa* helps in *kapha-shamana*. *Ananta* can help in mitigating CITs while preserving anticancer efficacy, enhancing quality of life and survival outcomes. Integrating *Ananta* within chemo-recovery protocols can offer evidence-based chemo-immunoprotection, bridging classical *Ayurvedic* pharmacodynamics with contemporary oncology to optimise breast cancer therapeutic outcomes.

ABBREVIATIONS

D&C – Doxorubicin and Cyclophosphamide; CIT – Chemotherapy-induced toxicities; QoL – Quality of life; CINV – Chemotherapy-induced nausea and vomiting; G-CSF – Granulocyte colony-stimulating factor; LVEF – Left ventricular ejection fraction; ACE – Angiotensin-converting enzyme; NK – Natural killer (cells); LAK – Lymphokine-activated killer (cells); DMBA – 7,12-Dimethylbenz[a]anthracene; TPA – 12-O-Tetradecanoylphorbol-13-acetate; ICD – Immunogenic cell death; RP-HPLC – Reverse-phase high-performance liquid chromatography; GST – Glutathione S-transferase; GSH – Glutathione; ROS – Reactive oxygen species.

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Conflicts of Interest

There are no conflicts of interest.

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