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Final Degree Thesis

Pharmacy Degree

PHYTOTHERAPY AS A STRATEGY TO MITIGATE THE TOXICITY OF CHEMOTHERAPY IN BREAST CANCER

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COMMEMORATY

To my **mummy**,
for her strength, her courage and her unconditional love.
This work stems from a desire to understand your struggle and transform pain into knowledge that can help other women overcome cancer with less suffering.
Thank you for being my inspiration every day.

ACKNOWLEDGEMENTS

This work would not have been possible without the unconditional support of the people around me, who have sustained me when I couldn't sustain myself and who have been a light in the darkest moments.

Thank you, especially to my partner, for being my refuge, my strength and my motivation. For believing in me when I doubted myself, for lifting me up unconditionally and for reminding me every day that I can do it. We have travelled this path together, and I will always go further if it is by your side.

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To my friends, who have been my chosen family, my companions in struggle, joy and silence. With you, I have learned that it is not blood that defines bonds, but presence, loyalty and unconditional love.

And finally, to my mother. With everything we have been through, I only hope that I have lived up to your example. I want you to feel proud, not only of this work, but of the woman I have become. Everything I do, I also do for you.

ABSTRACT

Phytotherapy as a Strategy to Mitigate the Toxicity of Chemotherapy in Breast Cancer

This Final Degree Project explores the toxicity associated with chemotherapy in breast cancer, with particular focus on the molecular mechanisms behind adverse effects and the potential of pharmacogenetics and phytotherapy to mitigate them without compromising antitumor efficacy.
A comprehensive literature review was conducted to analyse the systemic toxicity of commonly used chemotherapeutic agents—such as anthracyclines, taxanes, cyclophosphamide, fluorouracil, platinum compounds, and cyclosporines—and the underlying mechanisms, including oxidative stress, inflammation, and mitochondrial dysfunction.

The findings support the therapeutic potential of phytochemicals like *Platycodon grandiflorum*, curcumin, kaempferol, and β-elemene to reduce chemotherapy-induced toxicity through antioxidant, anti-inflammatory, and pro-apoptotic actions. Furthermore, pharmacogenetic markers in genes such as *RARG*, *SLC28A3*, and *CYP2C8* show promise in predicting individual susceptibility to adverse effects and in guiding personalised treatment.

The study concludes that integrating pharmacogenomics and phytotherapy into clinical oncology could enhance treatment adherence and patient quality of life. It emphasises the need for translational research and clinical validation to support a more predictive, preventive, and personalised therapeutic model.

Keywords: breast cancer, chemotherapy toxicity, pharmacogenomics, phytotherapy, natural compounds.

RESUM

La fitoteràpia com a estratègia per mitigar la toxicitat de la quimioteràpia en el càncer de mama.

Aquest treball de final de grau analitza la toxicitat associada a la quimioteràpia en el càncer de mama, amb especial atenció als mecanismes moleculars dels efectes adversos i al potencial de la farmacogenètica i la fitoteràpia per mitigar-los sense comprometre l'eficàcia antitumoral.

S'ha dut a terme una revisió exhaustiva de la literatura científica per analitzar la toxicitat sistèmica dels fàrmacs quimioteràpics més utilitzats —com les antraciclines, taxans, ciclofosfamida, fluorouracil, compostos de platí i ciclosporines— i els mecanismes fisiopatològics implicats, com l'estrès oxidatiu, la inflamació i la disfunció mitocondrial.

Els resultats sostenen el potencial terapèutic de compostos naturals com *Platycodon grandiflorum*, curcumina, kaempferol i β-elemene per reduir la toxicitat quimioteràpica mitjançant mecanismes antioxidants, antiinflamatoris i de modulació apoptòtica. A més, es destaquen marcadors farmacogenètics en gens com *RARG, SLC28A3* i *CYP2C8* amb capacitat predictiva individual i valor per a la personalització del tractament.

Es conclou que integrar la farmacogenòmica i la fitoteràpia en l'oncologia clínica podria millorar l'adherència al tractament i la qualitat de vida de les pacients. Es remarca la necessitat de recerca translacional i validació clínica per avançar cap a un model terapèutic més predictiu, preventiu i personalitzat.

Paraules clau: càncer de mama, toxicitat a la quimioteràpia, farmacogenòmica, fitoteràpia, compostos naturals.

INTEGRATION OF FIELDS

This final degree project falls mainly within the field of **Toxicology**, as its main objective is to study the adverse effects associated with chemotherapy treatment for breast cancer. Through an updated literature review, the toxicological mechanisms involved in the onset of systemic toxicities derived from the drugs used are analyzed. This approach allows for the practical application of knowledge acquired in toxicology, integrating concepts such as cellular toxicity, damage to healthy tissues, and the assessment of risks associated with drug treatment.

Secondly, the work is related to the subject of **Physiology and Pathophysiology**, since understanding the side effects requires a solid foundation in the normal functioning of the body and the pathological processes that result from alterations induced by external agents. The analysis of how these treatments affect different systems of the human body is supported by fundamental pathophysiological knowledge to interpret the clinical impact of chemotherapy.

Finally, it also integrates with **Pharmacology**, delving into aspects such as the mechanism of action of drugs, their metabolism, pharmacogenomics and therapeutic individualization. This approach allows the content of this subject to be applied in the context of the prevention and mitigation of toxicities, contributing to a more comprehensive and applied view of clinical pharmacology.

SUSTAINABLE DEVELOPMENT GOALS

The Sustainable Development Goals (SDGs), promoted by the United Nations, constitute a global roadmap for achieving a more just, healthy and sustainable future. This final degree project, which focuses on analysing the toxicity of chemotherapy treatments used in breast cancer and proposing strategies to reduce side effects, directly contributes to three of these goals: SDG 3, SDG 9 and SDG 12.

- SDG 3: Good health and well-being. This goal seeks to ensure healthy lives and promote well-being for all people and ages. The thesis is clearly aligned with this SDG, as its purpose is to improve the quality of life of breast cancer patients. Through a review of the scientific literature, the toxicity associated with common drugs such as anthracyclines, taxanes and 5-fluorouracil has been identified, and therapeutic alternatives such as phytotherapy and pharmacogenomics have been explored to mitigate adverse effects. These strategies optimise clinical outcomes while minimizing the negative impact of treatments.

- SDG 9: Industry, innovation and infrastructure. This goal promotes the development of resilient infrastructure, sustainable industrialization and innovation. The work contributes to this SDG by incorporating innovative techniques such as the use of iPSC-derived cell models to study cardiotoxicity, as well as the analysis of genetic polymorphisms to predict drug response. This approach represents a clear commitment to personalized medicine and translational research, which are essential areas for advancing towards a more modern and efficient healthcare system.

- SDG 12: Responsible consumption and production. This goal seeks to ensure sustainable consumption and production patterns. In this work, the potential of natural compounds such as curcumin, kaempferol and β-elemene to complement conventional treatments has been explored. The use of these substances can reduce the doses of chemotherapy required, thereby decreasing toxicity and the consumption of healthcare resources, with a positive impact on both patients and the healthcare system.

In short, this work contributes to a comprehensive and sustainable vision of health, promoting a safer, more innovative and responsible oncology model with the available resources.

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1. INTRODUCTION

1. Breast cancer

1.1. Incidence and mortality

In 2023, breast cancer accounted for nearly 30% of malignant tumours diagnosed in women in Spain, with approximately 35,300 new cases and 6,800 deaths, remaining the leading cause of cancer-related mortality among women. [1] Thanks to the implementation of population-based screening programmes and advances in imaging techniques and molecular diagnosis, five-year survival rates have improved to over 82%. [2]

1.1.1. Breast cancer physiology

The breast is made up of lobules and ducts, with each breast containing between 15 and 20 lobular sections. Each lobe has numerous small sections called lobelets, which ending dozens of milk-producing glands. These three structures are connected by narrow tubes called ducts, which transport milk toward the nipple. [3]

Each breast also contains blood and lymphatic vessels. The lymphatic vessels carry a colourless, watery fluid called lymph, which circulates between lymph nodes. Lymph nodes are small bean-shaped structures distributed throughout the body. They filter lymph and store white blood cells, which help fight infection and disease. Clusters of lymph nodes are found near the armpits (axillary nodes), under the arm, above the collarbone, and within the chest. [3]

There are two main types of breast cancer:

- Ductal carcinoma: This type begins in the milk ducts (and spreads outside the ducts to other breast tissues. It can also spread to other parts of the body through the blood and the lymphatic system. It is the most common type of invasive breast cancer.
- Lobular carcinoma: This type originates in the lobules (milk glands) of the breast and can spread to nearby breast tissues. In some cases, it also spreads to other parts of the body through the lymphatic and blood system.

Also noteworthy is inflammatory breast cancer, a rare and aggrieve type of very fast-growing breast cancer. It occurs when cancer cells block the lymphatic vessels in the skin of the breast, leading to inflammation. [3]

1.2. Breast cancer symptoms

Breast cancer in its early stages does not present any symptoms. For this reason, it is essential to have a regular and thorough medical check-up that will allow early detection of tumours that may not show obvious signs. [3]
As the disease progresses, symptoms may appear, such as:

- A lump in the breast or armpit, usually with an irregular shape and without pain.
- Changes in the size, shape, texture of the breast or nipple, including redness, skin dimpling or an orange peel-like textured appearance.
- Abnormal discharge from the nipple, which may be bloody, yellow, greenish or pus-like in appearance.

In more advanced stages, symptoms may include:
- Bone pain.
- Breathing difficulty.
- Swollen lymph nodes near the affected breast.
- Unexplained weight loss

1.3. Risk factors

Anything that increases the likelihood of developing a disease is known as a risk factor. However, having a risk factor does not necessarily mean that a person will develop cancer, while the absence of risk factors does not guarantee that a person will not develop the disease. **Figure 1** shows the main risk factors involved in breast cancer. [3]

1.3.1. Genetic factors

Breast cancer can be influenced by genetic factors. Genetic inheritance is thought to be involved in 5-10% of breast cancer. A genetic mutation in the *BRCA1* or *BRCA2* gene is the most frequent cause of hereditary breast cancer. According to statistics, a *BRCA1* mutation increases the risk of breast cancer by 55-65%, while a *BRCA2* mutation increases the risk by approximately 45%. [3]

1.3.2. Non-genetic factors

Breast cancer risk is also influenced by various non-genetic factors, including:

1.3.2.1. Pregnancy control and contraceptives

Women who have used oral contraceptives are slightly more likely to develop breast cancer. However, once treatment is stopped, the risk gradually reduces to normal. [3]

1.3.2.2. Overweight

Before menopause, most of the oestrogen is produced by the ovaries, with a small amount being produced in fatty tissue. During menopause, when the ovaries stop producing oestrogen, fat tissue becomes the primary source. As a result, having more fatty tissue after menopause increases the risk of breast cancer. [3]

1.3.2.3. Exposure to diethybestrol

Diethylbestrol was used between 1938-1971 to prevent miscarriages and other pregnancy-related issues. Women who took diethylbestrol during pregnancy were slightly more likely to develop breast cancer, and their children had a threefold risk ofstructural abnormality of the genitalia. [3]

1.3.2.4. Hormone replacement therapy after menopause

Oestrogens have been used to treat menopausal symptoms and prevent osteoporosis. However, long-term treatment with oestrogen (more than 15 years) is associated with an increased risk of breast and ovarian cancer. [3]

1.3.2.5. Other risk factors [3]

- A history of previous invasive, ductal or lobular breast cancer.
- Dense breast tissue observed on mammography.

- Exposure to high levels of naturally occurring oestrogen, which can result from:
  - Early onset of menstruation.
  - Having children at an advanced age or not having children.
  - Late menopause
  - Use of hormonal therapies with oestrogens and progesterone to treat menopausal symptoms.
- Frequent alcohol consumption.
- Advanced age, which is the main risk factor for the vast majority of carcinomas.

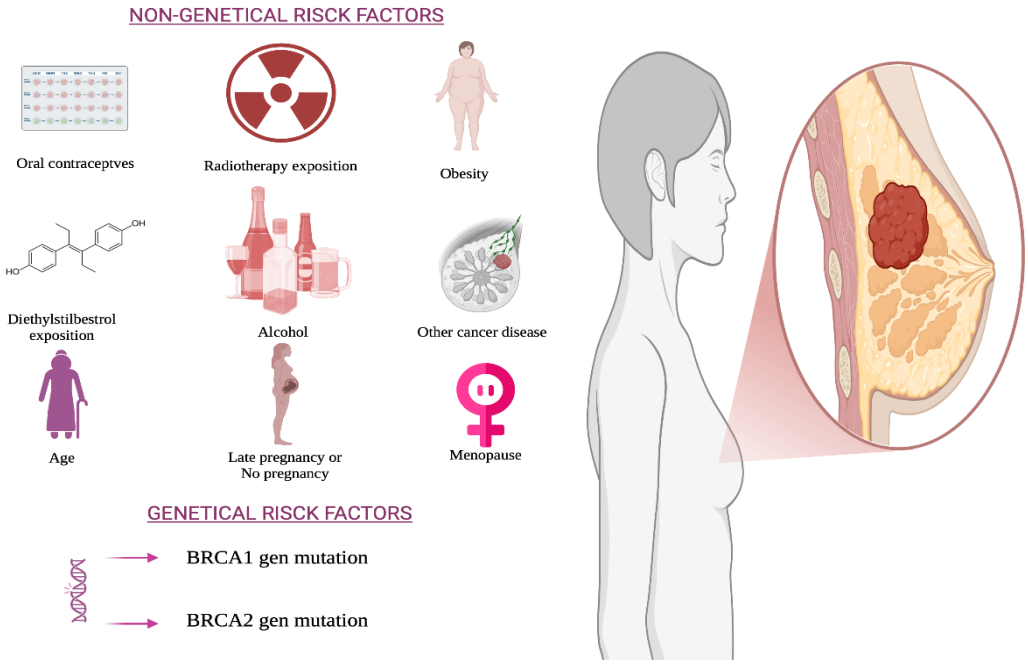

Figure 1. Risk factors to breast cancer. Created with BioRender.

1.4. Staging system

The staging system, which assesses the primary tumour stage, lymph node involvement, and distant metastasis, is used to determine the stage of the tumour. The TNM staging system is the most commonly used method for carcinoma cases. In this system, the letters correspond to: [4]

- **T**: Tumour - indicates the size and extent of the primary tumour.
- **N**: Node - indicates the number of nearby lymph nodes affected by cancer.
- **M**: Metastasis - indicates the presence of metastases. It will mean that the cancer has spread from the primary tumour to distant parts of the body.

Each component (T, N, M) is followed by a number or letter that provides further detail. [4]

Primary tumour (T):

- **TX**: The primary tumour cannot be assessed.
- **T0**: it is not possible to find the primary tumour.

- **T1, T2, T3,T4**: where T indicates the size or extent of the tumour. The higher the number, the larger or more invasive the tumour.

Regional lymph nodes (N):

- NX: Regional lymph nodes cannot be assessed.
- N0: No regional lymph node involvement.
- N1, N2, N3: Increasing involvement of regional lymph nodes. The higher the number, the more lymph nodes are affected and/or the greater the extent of spread.

Metastases distend (M):

- **MX**: Metastasis cannot be assessed.
- **M0**: No distant metastasis. The cancer has not spread to other parts of the body.
- **M1**: Distant metastasis is present. Cancer has spread to other parts of the body.

The possible TNM combinations can be grouped into five cancer stages. (**Table 1**)

- **Stage 0**: Abnormal cells are present but have not spread to nearby tissue. This stage is also called carcinoma *in situ*, this is not cancer yet but may become cancerous.
- **Stage I, II and IIII**: Cancer is present. The higher the number, the larger the tumour and the more it has spread into nearby tissues.
- **Stage IV**: The cancer has spread to distant parts of the body (metastasis).

1.5. Breast cancer treatment

A multidisciplinary approach combining local and systemic interventions is used in the treatment of breast cancer to maximize therapeutic efficacy and minimize patient harm. (**Table 1**) [5]

1.5.1. Surgery

Surgery is the cornerstone of local treatment and, in many cases, the first step after diagnosis. Breast conservation surgery (lumpectomy) consists of removing the malignant tumour along with a margin of healthy tissue, ensuring local control while preserving most of the mammary gland. When the characteristics of the tumour require it, a mastectomy is performed, which may be simple (complete removal of the breast) or modified radical (removal of the breast, nipple, areola and axillary nodes). During surgery, a sentinel lymph node biopsy is also performed, as previously described. [5]

1.5.2. Radiotherapy

As an adjunct to conservative surgery, external radiotherapy is administered to the breast or chest wall to eliminate microscopic residual disease and reduce the risk of local relapse. In cases of symptomatic bone metastasis, internal radiotherapy (brachytherapy) or radionuclides such as strontium-89 may be used to relieve pain and stop bone metastasis progression. [5]

1.5.3. Chemotherapy

Chemotherapy is a key component of treatment for intermediate to high-risk tumours, including HER2-positive and triple negative tumours. Triple-negative breast cancer is characterised by the absence of expression of oestrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER2). This tumour subtype tends to behave more aggressively, with a higher risk of recurrence and a higher prevalence in young women.
It can be used neoadjuvant (before surgery) to reduce tumour size and allow for less invasive surgery or adjuvant (after surgery) to eradicate micrometastases. Combined anthracycline and taxane treatments are the most common regimens, although the specific regimen will vary depending on the biological and clinical profile of each patient. [5]

1.5.4. Endocrine therapy

Indicated for hormone receptor-positive tumours (estrogen and/or progesterone) , endocrine therapy works by reducing the production or blocking the action of hormones that stimulate tumour growth. Options include aromatase inhibitors (anastrozole, letrozole), selective estrogen receptor modulators (tamoxifen) and gonadotropin-releasing hormone agonists (goserelin, leuprorelin). Their prolonged administration sometimes exceeds five years, to minimize the risk of late recurrence. [5]

1.5.5. Targeted therapy

Targeted therapy is based on the identification of tumour-specific molecular alterations – such as, HER2 overexpression or *BRCA* gene mutations. Options include monoclonal antibodies (trastuzumab, pertuzumab) and small-molecule tyrosine kinase inhibitors (lapatinib, neratinib, tucatinib). These drugs selectively target altered signaling pathways in cancer cells, reducing the impact on healthy tissue. [5]

1.6.6. Immunotherapy

Although still under development, immune checkpoint inhibitors (e.g. pembrolizumab) have shown benefits in selected subgroups of breast cancer patients with high mutational burden or an active immunogenic microenvironment, by enhancing the T-cell-mediated antitumour response. [5]

In summary, a personalized combination of these treatment modalities - selected according to tumour stage, molecular profile and patient characteristics - is the optimal strategy for achieving effective local and systemic disease control, while minimizing toxicities and improving quality of life.

STAGE	CLASSIFICATION	SURGERY	RADIOTHERAPY	ENDOCRINE	IMMUNO	CHEMOTHERAPY	RELATIONSHIP WITH BIOMARKERS	MAIN SIDE EFFECTS
0(DCIS) Ductal carcinoma in situ	Non-invasive, confined to the ducts	Lumpectomy or mastectomy	Yes (If the case is lumpectomy)	Yes (for ER+)	It is not usual	It is not usual	ER+: 5 years of tamoxifen (premenopausal) or AI/tamoxifen (postmenopausal)	Radiotherapy: skin erythema, fibrosis Tamoxifen: hot flushes, thrombosis, risk of endometrial cancer IA: osteoporosis, fractures, myalgias
I-II Primary invasive	Limited tumour, negative or minimal nodules	Lumpectomy or mastectomy	Yes	Yes (for HR+)	Yes (If the case is ERBB2+)	According to the molecular profile	HR+: tamoxifen or IA (up to 10 years) HER2+: trastuzumab (1 year) Triple negative: chemo alone	Tamoxifen: hot flushes, thrombosis, uterine cancer IA: osteoporosis Chemo (taxanes, anthracyclines): nausea, alopecia, myelosuppression, neuropathy, cardiotoxicity Trastuzumab: cardiac dysfunction
III Locally advanced	Large tumour or clinically positive lymph nodes	Mastectomy + axillary dissection	Yes	Yes (for HR+)	Yes (If the case is ERBB2+)	Yes	Targeted therapy according to HR / HER2 / triple-negative HER2+: trastuzumab ± pertuzumab/ neratinib combination	Radiotherapy: skin toxicity, fibrosis Chemo: neuropathy, alopecia, myelosuppression, cardiotoxicity (anthracyclines) Trarstuzumab/pertuzumab: cardiac dysfunction Neratinib: severe diarrhoea Endocrine: same as in stages I-II
IV Metastatic	Disseminated cancer (bone, hepatic, pulmonary, cerebral)	Variable (if the quality of life improves)	Yes (if there is a high tumour burden)	Yes (for HR+)	Yes (If the case is ERBB2+)	Yes	Therapy selected exclusively according to tumour biomarkers	Endocrine: as in previous stages Trastuzumab / pertuzumab / neratinib: fatigue, diarrhoea, cardiac toxicity Chemotherapy: cumulative effects (myelosuppression, nausea, severe fatigue) Denosumab/ bisphosphonates: osteonecrosis of the jaw, hypocalcaemia, diarrhoea, fatigue.

Table 1. Cancer treatments according to breast cancer stage. The table shows the therapeutic options (surgery, radiotherapy, endocrine therapy, immunotherapy, and chemotherapy) based on the stage of the cancer, along with their relationship to biomarkers and the most common side effects. Adapted to illustrate the multidisciplinary approach to breast cancer treatment. [6,7]

2. OBJECTIVES AND HYPOTHESIS

Based on the current understanding of chemotherapy-induced toxicity and individual genetic variability in breast cancer patients, we hypothesize that the identification of predictive genetic biomarkers, in combination with targeted protective interventions, mainly based on phytotherapy, can significantly reduce the incidence and severity of toxicities without compromising the anti-tumour efficacy of chemotherapy.

To explore this hypothesis, the following objectives have been defined:

1. To characterize the cellular and molecular mechanisms of chemotherapy-induced toxicity.

2. To identify predictive biomarkers of toxicity by analysing polymorphisms in genes involved in drug metabolism and DNA repair.

3. To evaluate protective strategies in experimental models, testing antioxidant agents and apoptosis modulators for their compatibility with anti-tumour efficacy.

4. To assess the longitudinal clinical impact of toxicity, measuring quality of life, organ function, and survival outcomes over time.

5. To explore phytotherapeutic approaches for the reduction and/or palliation of chemotherapy-related toxicity.

3. MATERIALS AND METHODS

This study is a narrative literature review aimed at identifying the toxicological effects associated with chemotherapeutic agents used in breast cancer treatment, and at developing a therapeutic guide to reduce, mitigate, and prevent such toxicity.

The literature search was primarily conducted through reputable scientific databases, including PubMed and Scopus, known for their rigorous peer-reviewed content. Access to these databases was provided through the University of Barcelona's CRAI (Learning and Research Resources Centre).

To ensure the quality and relevance of the selected publications, advanced search strategies were employed using combinations of keywords such as "breast", "toxicity", "cancer", "chemotherapy", and "adverse effects". The review was limited to articles published from 2019 onwards, in order to prioritise recent evidence and current therapeutic approaches.

The development of the therapeutic guide and the clarification of specific clinical concepts were supported by expert Dr. Patricia Gómez, a practicing oncologist.

Finally, the visual materials and infographics included in this study were designed using digital platforms such as Canva and BioRender, which enabled the clear and effective presentation of complex concepts.

4. RESULTS

This section outlines the main chemotherapeutic treatments used in breast cancer management, focusing on the most commonly administered agents, including anthracyclines, cyclophosphamide, taxanes, fluorouracil, cyclosporines, and plasticizer derivatives. While these drugs are effective in targeting cancer cells, they are often associated with significant toxicity that can adversely affect patients' quality of life. Therefore, we will also examine the available phytotherapeutic strategies aimed at mitigating these adverse effects, with the goal of improving treatment tolerance and adherence.

4.1. Anthracyclines

Anthracyclines, such as doxorubicin and epirubicin, are DNA intercalating agents that insert themselves between nitrogenous bases and inhibit the activity of topoisomerases, causing double-stranded DNA breaks. They also generate free radicals that damage DNA and cellular membranes. These cytotoxic effects occur primarily during the S phase of the cell cycle, which explains their anti-tumor potential. [8]
Breast cancer is one of the most relevant clinical settings for studying anthracycline-induced toxicity. Breast cancer patients commonly receive doxorubicin or epirubicin, drugs with high efficacy but with a significant risk of cardiotoxicity. [8]

4.1.1. Anthracyclines toxicity

To investigate anthracycline-induced cardiotoxicity (AIC), several studies have used cardiomyocytes derived from induced pluripotent stem cells (hiPSC-CMs) from breast cancer patients treated with anthracyclines. [9] These in vitro models reproduced the differential susceptibility to cardiotoxicity, highlighting hiPSC-CM cells as a predictive model and as a tool for pharmacological trials within a personalized context. Interestingly, cardiomyocytes from patients who developed AIC showed [9]:

- Increased reactive oxygen species (ROS) production.
- Sarcomeric structural damage
  Alteration in the use of intracellular calcium.
- Increased apoptosis in response to doxorubicin.

On the other hand, there are several relevant genetic variants have been identified in breast cancer patients with relevance to AIC. Several studies have identified genetic variants that predispose patients treated with anthracyclines to cardiotoxicity. In the case of POLRMT, the rs62134260 polymorphism has been significantly associated with AIC in breast cancer patients treated with epirubicin, probably due to its effect on mitochondrial expression and its involvement in cardiac dysfunction. On the other hand, the SNP rs2229774 in the RARG gene is linked to an increased risk of doxorubicin-induced AIC, due to its role in the regulation of TOP2B, a key gene in cardiomyocyte DNA damage. In addition, RARG agonists such as CD1530 or ATRA have shown cardioprotective effects. Finally, a variant in SLC28A3, a gene that encodes a nucleoside transporter, can alter the entry of doxorubicin into cardiomyocytes, thus modulating its toxicity.[9]

4.1.2. Phytotherapy for AIC

AIC is a major concern in breast cancer treatment. This section explores the potential of *Platycodon grandiflorum (P. grandiflorum),* a medicinal plant, as a phytotherapeutic agent to prevent this toxicity

From a phytotherapeutic perspective, *P. grandiflorum* shows promise in preventing AIC due to the following mechanisms:

- **Antioxidant properties**: evidence indicates that *P. grandiflorum* possesses the ability to reduce the formation of ROS and prevent lipid peroxidation. Given that excessive ROS generation is the most accepted hypothesis to explain the cardiac toxicity of anthracyclines, these antioxidant properties may represent the main mechanism by which the plant could protect the myocardium. [10]
- **Nitric oxide (NO) regulation:** Studies indicate that *P. grandiflorum* can help maintain adequate levels of NO in cardiac cells, avoiding both excess and deficiency of this molecule, which can compromise myocardial function. Timely and balanced NO regulation can reduce oxidative stress and improve vasodilation, thus contributing to cardiovascular protection. [10]
- **Anti-inflammatory properties**: In vitro evidence shows that compounds contained in *P. grandiflorum* have modulating effects on inflammatory processes and on the oxidative stress cascade, which is relevant in the context of chemotherapy-induced toxicity. [10]

In the context of breast cancer, a randomized, double-blind, placebo-controlled, single-center clinical trial was conducted to evaluate the cardioprotective effects and safety of *Platycodon grandiforum* granules versus placebo in patients with early-stage breast cancer receiving anthracycline-based chemotherapy. A total of 120 patients were assigned to receive either *P. grandiflorum* granules or placebo twice daily for 12 weeks. [10]

The primary outcome was the incidence of heart failure, and secondary outcomes include mortality, electrocardiographic findings, cardiac function, and cardiac biomarkers. Assessments were be performed at baseline and at 3, 6, 9, 12, 16 and 20 weeks after randomization. The study defines the primary outcome as the onset of heart failure (clinical or subclinical), assessed using the NYHA classification and left ventricular ejection fraction (LVEF) by MUGA scan. Secondary outcomes include all-cause mortality, cardiac death, ECG abnormalities, ventricular diastolic function, echocardiographic parameters, and cardiac biomarkers (troponin I, BNP, and CK-MB). Safety outcomes comprise routine clinical and laboratory evaluations. [10]

In conclusion, *P. grandiflorum* shows potential as a phytotherapeutic to mitigate cardiotoxicity during anthracycline-based chemotherapy, primarly through its antioxidant and NO-regulating effects. However, evidence in humans is still limited, and its integration into oncological therapies requires further clinical validation and standardized extract formulations to ensure safety and efficacy. [10]

4.2. Taxanes

Paclitaxel and docetaxel, two taxanes widely used in the treatment of breast cancer, share a common mechanism of action based on the stabilization of cellular microtubules. Both agents bind to beta-tubulin, promoting polymerization and preventing microtubule depolymerization, which leads to the arrest of the cell cycle in the G2/M phase and consequently to tumor cell apoptosis induction. [11]
Although they are structurally similar, these drugs present important differences in their pharmacological behavior. Docetaxel shows a higher affinity for the tubulin binding site, as well as a longer intracellular retention and a higher concentration within the target cells compared to paclitaxel. Moreover, docetaxel induces in a much more potent way the phosphorylation and consequent inactivation of the antiapoptotic BCL-2 protein, thus promoting tumor apoptosis. [11]

4.2.1. Taxanes toxicity

Regarding toxicity, paclitaxel and docetaxel present different adverse effect profiles. Docetaxel is associated with a more pronounced hematologic toxicity than paclitaxel. In studies in which both drugs were combined with doxorubicin in patients with metastatic breast cancer, grade 3-4 neutropenia was significantly more frequent with docetaxel. In contrast, paclitaxel is more likely to cause grade 2 to 4 sensory peripheral neuropathy, especially when administered weekly. This neurosensory toxicity can be cumulative and, may limit the continuation of treatment. [12]

Taxanes disrupt microtubule dynamics, affecting axonal transport and altering ion channel activity. This leads to hyperexcitability of peripheral neurons due to changes in sodium and potassium channel expression and function. Additionally, taxanes are related to mitochondrial disorders causing an increase in the production of ROS, resulting in damage to proteins, enzymes, and lipids. This dysregulation of neuronal homeostasis can promote apoptosis and demyelination of peripheral nerves. [12]
However, comparative studies have shown that both taxanes offer similar clinical efficacy when combined with doxorubicin for the treatment of metastatic breast cancer, though they differ in their toxicity profiles. [12]

Furthermore, taxanes activate astrocytes and microglia, which further attracts immune cells, causing the release and increase of proinflammatory cytokines. This leads to a sensitization of nociceptors and causes an overexcitation of peripheral neurons causing neuroinflammation. [13]

A relevant aspect would be found in personalized pharmacogenetics. By analizing specific single nucleotide polymorphisms (SNPs) it may be possible to predict which patients may have a higher risk of toxicity, allowing for dose adjustments of the treatments or choose alternative regimens. However, most studies are retrospective and have limited sample sizes. [14]
Taxane-induced toxicities may be modulated by specific genetic variants, as detailed in **Table 2**.

GEN	SNP	ASSOCIATED TOXICITY
ABCB1	rs1045642	Peripheral neuropathy wiht increased neuronal exposure to paclitaxel
ABCB1	rs1128503	Peripheral neuropahty due to alteration in drug transport
CYP2C8	rs10509681	Peripheral neuropathy due to slow paclitaxel metabolism
CYP2C8	rs11572080	Peripheral neuropathy due to slow paclitaxel metabolism
EPHA5	rs7349683	Gross sensory neuropathy
TUBB2A	rs909965	Neuropathy due to microtubular dysfunction
CYP3A4/5	rs776746	Neutropenia due to altered metabolism of docetaxel
ABCB1	rs2032582	Severe neutropenia
SLCO1B3	rs11045585	Neutropenia due to altered hepatic drug elimination

Table 2. Genetic variants (SNPs) associated with taxane-induced toxicities. The table shows different single nucleotide polymorphisms (SNPs) in genes involved in drug transport, metabolism, or elimination, and their relationship with common adverse effects, such as peripheral neuropathy and neutropenia, in patients treated with paclitaxel or docetaxel. [14]

4.2.2. Phytotherapy for taxane toxicity

In the context of chemotherapy-induced toxicity, there is an emerging interest in exploring natural compounds that can enhance the antitumor efficacy of taxanes and at the same time, reduce their toxicity. One study analyzed the therapeutic potential of *Hibiscus rosa-sinensis* extract as a chemotherapeutic adjuvant. On with breast cancer cell lines and normal cells to evaluate the cytotoxicity of the extract. The techniques used included cell viability assays, apoptosis analysis and co-treatment studies with chemotherapeutics. [15]

The results showed:

- Selective apoptosis induced by Hibiscus: Hibiscus extract demonstrated a significant ability to induce apoptosis in tumor cells, without substantially affecting normal mammary cells. This may suggest another tumor speciality, a crucial property for any adjuvant agent. [15]
- Positive interaction with Paclitaxel: one of the most important findings of the study was the synergy observed between Hibiscus extract and Paclitaxel. The combination resulted in a greater inhibition of tumor growth compared to the monotherapy of the drug. This synergistic effect is confirmed by a combination index (CI<1). This synergy makes it possible to reduce the dose of Paclitaxel without compromising its efficacy, which would potentially reduce the incidence of adverse effects related to its cumulative toxicity. [15]
- Possible reduction of toxicity: although the study does not directly evaluate toxicity parameters in animal or human models, but the fact that it is possible to acquire the same antitumor effect at lower doses of Paclitaxel, thanks to the combined use with *hibiscus,* has clear implications to mitigate peripheral neuropathy, leukopenia and other typical dose-dependent toxicities of taxanes. [15]

Therefore, this study provides promising preclinical evidence that hibiscus flower extract not only has selective cytotoxic properties against breast cancer cells, but also interacts synergistically with paclitaxel, which allows a reduction of therapeutic doses. This reduction leads to the possibility of minimizing the severe side effects, thus improving the quality of life of cancer patients. [15]

Berberine, an isoquinoline alkaloid of plant origin, has shown promising properties as an adjuvant agent. In a recent study, a joint release system in nanoparticles was designed that combines paclitaxel and berberine. This strategy not only allowed for greater selective accumulation in tumour tissue, but also improved therapeutic efficacy by generating a synergistic effect between the two compounds. Thanks to this synergy, it was possible to reduce the necessary doses of paclitaxel, thus minimising its toxic effects. In addition, the nanomicelle system prevented the accumulation of the drug in unwanted tissues, significantly reducing damage to organs such as the lungs and preventing weight loss in the treated animal models. Therefore, berberine, in combination with paclitaxel within a targeted delivery system, indirectly contributed to reducing the toxicity of taxane in the treatment of triple-negative breast cancer. [16]

Complementarily, another study focusing specifically on paclitaxel-induced neurotoxicity demonstrated that berberine also has direct protective effects against this toxicity. In a mouse model, repeated administration of paclitaxel induced peripheral neuropathy, manifested as

thermal hyperalgesia. The application of a single dose of berberine, at different concentrations, was sufficient to significantly reduce this hypersensitivity to pain. The authors attribute this effect to the antioxidant and anti-inflammatory properties of berberine, which acts by decreasing the production ROS and the release of inflammatory cytokines. This finding is particularly relevant, as taxane-induced neuropathy is one of the most common and limiting toxicities in clinical practice. Unlike the previous study, here it is shown that berberine, administered alone and without the need for advanced delivery systems, can exert a direct neuroprotective effect against paclitaxel-induced toxicity. [17]

The studies analysed highlight the potential of natural compounds such as *Hibiscus rosa-sinensis* extract and berberine as adjuvants in taxane treatments. Both show synergistic effects with paclitaxel, allowing for reduced doses without compromising antitumour efficacy, which could significantly decrease its toxicity. In addition, berberine demonstrates a direct protective effect against paclitaxel-induced neuropathy, underscoring its value in both therapeutic efficacy and improving patient quality of life.

4.3. 5-Fluorouracil

5-Fluorouracil (5-FU) has been a cornerstone in the chemotherapeutic treatment of breast cancer for decades, especially in the adjuvant setting, i.e., administered after surgery with the aim of eliminating residual tumour cells and reducing the risk of relapse. 5-FU exerts its cytotoxic effect through three main mechanisms: incorporation into RNA, incorporation into DNA, and inhibition of thymidylate synthase (TS), an enzyme essential for DNA nucleotide synthesis. Traditionally, 5-FU has been part of chemotherapy regimens such as CMF (cyclophosphamide, methotrexate, and 5-FU) and FEC/FAC (5-FU together with epirubicin or doxorubicin and cyclophosphamide. [18]

4.3.1. 5-FU Toxicity

From a pathophysiological point of view, the main toxicities associated with 5-FU affect the hematologic, gastrointestinal, hepatic and renal systems.

4.3.1.1. Hematological toxicity

5-FU induces a marked myelosuppression, affecting the bone marrow and reducing the production of blood cells. [In animal models – specifically in Wistar rats with dimethylhydrazine-induced colorectal cancer - a significant decrease in the number of erythrocytes, hemoglobin levels, and platelets was observed. [19]
This hematopoietic suppression leads to anemia, thrombocytopenia and often severe immunologic compromise, increasing susceptibility to infection. [19]

4.3.1.2. Gastrointestinal toxicity

Among the most common adverse effects of 5-FU are mucositis, diarrhea, and stomatitis, resulting from damage to the epithelial cells of the gastrointestinal tract. [20]
Mucositis refers to the inflammation and ulceration of the mucous membranes lining the digestive tract, while stomatitis specifically affects the oral cavity, causing pain, redness, and sores. These conditions not only compromise the absorption of nutrients, but also lead to a decrease in appetite and food intake, further deteriorating the patient's overall condition. [20]

4.3.1.3. Hepatotoxicity

The liver, as the primary organ responsible for 5-FU metabolism, is particularly susceptible to its toxicity. Significant increases in liver enzyme levels such as ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), ALP (Alkaline Phosphatase) and GGT

(Gamma-Glutamyl Transferase) have been observed in animals treated with 5-FU, indicating hepatocellular damage. [20]
In addition, histological analyses further reveal loss of hepatocellular architecture, necrosis, fibrosis and inflammatory infiltration, confirming the hepatotoxic nature of the drug. [20]

4.3.1.4. Nephrotoxicity

The kidneys are also involved in the elimination of 5-FU and prolonged exposure to the active metabolite can lead to renal dysfunction. [20]
In animal models, increased levels of urea, blood urea nitrogen (BUN) and serum creatinine have been documented, accompanied by histological lesions such as glomerular degeneration, vascular congestion, tubular necrosis and inflammatory cell infiltration. [20]

4.3.2. Phytotherapy for 5-FU toxicity

4.3.2.1. β-elemene

The role of the natural compound β-elemene extracted from *Curcuma wenyuin* has been evaluated as a coadjuvant to potentiate the action of 5-FU in triple-negative breast cancer cells by modulating several signaling pathways involved in cell proliferation, apoptosis and survival. [21]

5-Fluorouracil (5-FU) acts by inhibiting thymidylate synthase, which interferes with DNA synthesis in tumour cells. However, its efficacy in triple-negative breast cancer (TNBC) is limited due to the compensatory activation of cell signalling pathways such as PI3K/AKT, RAF-MEK-ERK and NF-κB poor induction of apoptosis when used as monotherapy, and the possibility of developing acquired resistance. [21]

In this context, the combination of 5-FU with β-elemene, a natural sesquiterpene with antitumour activity described in various cell models, has been investigated. The study analysed demonstrated that this combination exerts synergistic effects on tumour growth by inhibiting the main signalling pathways related to cell proliferation and survival. A decrease in AKT phosphorylation, inhibition of the RAF-MEK-ERK pathway and inactivation of NF-κB were observed, which favoured an increase in tumour apoptosis. [21]

Likewise, the combined treatment increased the expression of proapoptotic proteins such as caspase-3, caspase-9 and Bax, and reduced the levels of Bcl-2, involved in the inhibition of apoptosis, indicating a clear activation of the mitochondrial apoptotic pathway. In both in vitro models and animal studies, this combination showed greater inhibition of cell proliferation compared to either compound alone. [21]

Although the study did not specifically focus on evaluating the toxicity of 5-FU, the data suggest that the combination allows for lower doses of the drug to be used without compromising its efficacy, which could translate into a reduction in typical adverse effects such as mucositis, hepatotoxicity, or myelosuppression. Furthermore, in the in vivo model with BALB/c mice, no visible signs of toxicity or significant body weight loss were detected, indicating good tolerability of the combination treatment. [21]

This evidence raises the possibility of incorporating β-elemene as an adjuvant agent in future treatment protocols and underscores the importance of exploring strategies based on natural products to optimize the efficacy and safety of classical chemotherapeutic drugs. [21]

4.3.2.2. Curcumin and berberine

Ziasarabi et al. (2021) investigated the synergistic effect of curcumin and berberine, both formulated in nanomicelles, in combination with 5-FU on MCF-7 breast cancer cells. Various in vitro assays were conducted to evaluate the effects of the combination on cell viability, apoptosis, cell migration and the expression of cell death regulator. [22]

The results showed that both curcumin and berberine, when administered individually, exerted moderate antitumor effects. However, when combined with 5-FU, a significantly greater reduction in cell viability was observed compared to treatment with 5-FU alone. The triple combination (5-FU + nanomicellar curcumin+ nanomicellar berberine) produced the most potent cytotoxic effect, suggesting a clear synergy between the natural compounds and the chemotherapeutic agent. [22]
Moreover, apoptosis induction was markedly enhanced in the combination groups. This was evidenced by increased expression of pro-apoptotic genes such as *p53* and *Bax*, and activation of caspases 3 and 9, indicating involvement of the intrinsic mitochondrial pathway. Concurrently, a downregulation of the anti-apoptotic gene *Bcl-2* was observed, further promoting programmed cell death. [22]

In addition to cytotoxic effects, the combinations significantly inhibited cell migration, an important factor in cancer metastasis. A wound healing assay revealed that cells treated with the triple combination exhibited a notably reduced migratory capacity compared to those treated with individual agents.[22]

A noteworthy aspect of this study is the use of nanomicellar formulations for curcumin and berberine. These structures improve solubility, stability, and bioavailability, likely explaining the enhanced efficacy observed in the combination therapies. By facilitating intracellular delivery and protecting the compounds from degradation, nanomicelles boost therapeutic potential without increasing dosage.[22]
In conclusion, the co-administration of nanomicellar curcumin and berberine with 5-FU significantly enhances antitumor efficacy, induces apoptosis, and inhibits migration in MCF-7 breast cancer cells. These findings suggest that such combinations could allow for lower doses of 5-FU, potentially reducing systemic toxicity and improving clinical outcomes in breast cancer treatment. [22]

4.3.2.3. Kaempferol

Kaempferol (KMP) is a natural flavonoid found widely found in fruits and vegetables such as cabbage, broccoli, peppers, root vegetables and citrus fruits. Its phenolic structure confers antioxidant and anti-inflammatory properties, as well as anti-apoptotic, anti-tumor and immunomodulatory effects. In this context, Sharma et al. (2024) evaluated the ability of KMP to mitigate the toxic effects induced by 5-FU in an experimental rat model of colorectal cancer. [23]
Where the results showed:

- Hematologic protection: Coadministration of KMP with 5-FU led to a significant restoration of altered hematologic parameters. Improvements in the levels of erythrocytes, hemoglobin and platelets was observed, indicating a hematoprotective activity. This effect may be due to the ability of KMP to stimulate erythropoiesis and thrombopoiesis, as well as to reduce oxidative stress on hematopoietic progenitor cells in the bone marrow. [23]
- Gastrointestinal protection: In the intestinal epithelium, KMP showed an evident protective action. Histological analysis of intestinal tissue showed reduced inflammation, absence of necrosis, and preserved crypt architecture in the KMP - treated groups. Moreover, animals exhibited improved appetite and increased food and water intake, suggesting functional recovery of the gastrointestinal system. [23]

- Hepatic protection: KMP also showed hepatoprotective effects. Animals treated with KMP exhibited reduced levels of liver enzymes elevated by 5-FU and partial normalization of bilirubin. Histologically, KMP preserved liver architecture and reduced signs of inflammation and fibrosis. These effects are likely due to its antioxidant capacity, which shields hepatocytes from chemotherapy-induced oxidative damage. [23]
- Renal protection: Finally, KMP provided notable protection against 5-FU-induced renal injury. Treated animals showed normal or near-normal levels of urea and creatinine. Histological findings indicated reduced structural damage in glomeruli and renal tubules, along with decreased inflammatory cell infiltration—particularly in groups receiving low-dose 5-FU combined with KMP. [23]

4.3.2.4. Thymoquinone nanoemulsion

One of the most relevant studies in this field evaluated the cardioprotective effect of thymoquinone in nanoemulsion form (NTQ) against 5-FU-induced cardiotoxicity in rats. The experimental design included five groups of animals, including one group treated exclusively with 5-FU and two groups that received NTQ (at doses of 2 and 10 mg/kg) concomitantly with the chemotherapeutic agent. Multiple parameters were evaluated: electrocardiographic, biochemical, markers of oxidative stress and histological damage to cardiac tissue. [24]

The results showed that treatment with 5-FU produced significant alterations in cardiac function and structure, such as ST segment and QTc interval prolongation, increased cardiotoxic enzymes, and increased lipid peroxidation. Co-administration with NTQ normalised electrocardiographic parameters, reduced serum biomarkers of myocardial damage, restored antioxidant balance and preserved the histological architecture of cardiac tissue. [24]

These observations indicate that thymoquinone acts as a direct cardioprotective agent against 5-FU toxicity without requiring a reduction in the dose of the chemotherapeutic agent. The protective effect appears to be mediated mainly by its antioxidant and anti-inflammatory properties, neutralising the oxidative damage associated with 5-FU. This finding suggests that thymoquinone may represent a promising therapeutic strategy to mitigate adverse cardiovascular effects in patients undergoing fluoropyrimidine chemotherapy and highlights the need for future research in clinical models to validate its safety and efficacy in humans. [24]

4.3.2.5. Astaxanthin

Among phytotherapeutic compounds with the potential to reduce the adverse effects of chemotherapy, astaxanthin has demonstrated a direct hepatoprotective effect against 5-FU-induced toxicity. In the experimental study conducted by Öztürk et al. (2025), this capacity was evaluated in an animal model using albino rats. [25]
The study design included five experimental groups: a control group, a group treated with astaxanthin alone (32 mg/kg), a group treated exclusively with 5-FU (100 mg/kg), and two groups that received astaxanthin at doses of 16 or 32 mg/kg concomitantly with 5-FU for a period of 14 days. Hepatic biochemical parameters, biomarkers of oxidative stress, markers of apoptosis, and hepatic histological damage were analysed.[25]
The results showed that 5-FU administration induced severe hepatotoxicity, evidenced by significant elevations in liver enzymes increased malondialdehyde (MDA), decreased endogenous antioxidants and overexpression of inflammatory cytokines and markers of genetic damage. Co-administration with astaxanthin significantly reversed these alterations, especially at high doses, restoring redox balance, reducing inflammation and preserving liver structure.

These findings support the potential use of astaxanthin as a hepatoprotective adjuvant in fluorouracil treatments, allowing the toxic impact of chemotherapy to be reduced without the need to modify its dosage. However, the need for additional clinical studies to validate these effects in humans is emphasised. [25]

Finally, a systematic review article compiles evidence on the combined use of 5-FU with various phytotherapeutic compounds, such as curcumin, resveratrol, quercetin, and epigallocatechin-3-gallate (EGCG), to enhance the antitumour effect and reduce toxicity. It is described that these natural agents can attenuate common adverse effects of 5-FU, including mucositis, hepatotoxicity, and myelosuppression, through antioxidant, anti-inflammatory, and modulation mechanisms of cellular signalling pathways involved in apoptosis and tissue damage. [26]
Although the article does not include direct experimentation, it compiles evidence from multiple preclinical studies suggesting that these phytochemicals not only increase the antitumour efficacy of 5-FU but also directly reduce its toxicity to healthy tissues, thereby improving the therapeutic profile of the treatment. [26]

4.4. Cyclosporines

The treatment of breast cancer has evolved considerably in recent decades. In this context, recent research has proposed new therapeutic applications for traditional drugs, such as cyclosporine A (CsA). Originally used as an immunosuppressant in transplant patients, CsA has shown the ability to inhibit tumor cell growth. [27]

Jiang et al. (2012) investigated the ability of CsA to inhibit breast cancer cell proliferation through the suppression of Pyruvate kinase M2 (PKM2) expression, a protein involved in cellular biosynthesis that supports the uncontrolled proliferation characteristic of cancer. For this purpose, three representative breast cancer cell lines, -MCF-7, MDA-MB-435 and MDA-MB-231- were used, along with normal mammary epithelial cells (HBL-100) as a control. The results showed that CsA significantly reduced the viability of tumor cells in a time- and dose-dependent manner, while the effect on normal cells was limited. This suggests selective toxicity, a critical feature for minimising systemic side effects. [27]

Mechanistically, the inhibitory effect of CsA was related to a decrease in PKM2 expression, both at mRNA and protein level. This reduction was accompanied by a drop in PKM2 enzymatic activity and, consequently, a significant decrease in intracellular ATP production. [22]
Additionally, by flow cytometry analysis, it was observed that CsA induces cell necrosis, not apoptosis, as the predominant form of cell death. This finding is important because many conventional cancer therapies lose efficacy in apoptosis-resistant tumors. [27]

Clinically, these findings suggest a novel role for CsA—not as an immunosuppressant, but as a metabolic disruptor that weakens tumor cell bioenergetics and promotes their destruction. Although the results are based on in vitro models, they open the door to new therapeutic strategies targeting cancer metabolism in breast cancer. [27]

4.4.1. Cyclosporine Toxicity

Although CsA has emerged as an agent of interest in oncology due to its ability to modulate the immune system and reverse mechanisms of resistance to chemotherapy; its clinical application in oncology patients is limited by a range of significant adverse effects, well-documented in preclinical and clinical studies. [28]

4.4.1.1. Nephrotoxicity

Nephrotoxicity is one of the most severe and frequent adverse effects of CsA. Specifically, CsA causes vasoconstriction of renal arteries, activation of proinflammatory pathways and oxidative stress, which contributes to progressive structural renal damage. Both animal and human studies have shown that prolonged administration of CsA can lead to dose-dependent and potentially irreversible renal fibrosis. [28]

4.4.1.2. Hepatotoxicity

CsA can also induce hepatic alterations, such as elevated transaminases and histological damage to liver tissue. These effects are exacerbated when combined with other hepatotoxic agents, which represents a frequent situation in oncological patients receiving multiple drugs. [28]

4.4.1.3. Neurotoxicity

Another relevant adverse effect is cyclosporine-induced neurotoxicity. Fojnica et al. (2024) demonstrated that CsA treatment promotes several neurological disorders such as tremors, headaches, visual disturbances, seizures and even the development of posterior reversible encephalopathy syndrome (PRES). These neurological complications are clinically significant as they may occur even at therapeutic plasma concentrations. [28]

4.4.1.4. Arterial hypertension

CsA interferes with hemodynamic regulation by inducing systemic vasoconstriction, especially in the renal vasculature, which contributes to the development of hypertension. This condition can appear acutely or chronically and requires pharmacological intervention for its management. [28]

4.4.1.5. Immunosuppression and risk of infections

CsA suppresses the function of T lymphocytes. While this can be beneficial by reducing regulatory T cells (Tregs) within the tumor microenvironment, it also significantly weakens the body's immune defense. This increases the risk of opportunistic infections and can worsen outcomes in immunocompromised cancer patients. [28]

4.4.1.6. Risk of secondary neoplasms

One of the most concerning adverse effects discussed in the review is the potential development of secondary malignancies associated with long-term CsA use. Transplant patients treated with CsA have shown a higher incidence of lymphomas, skin carcinomas, and other solid tumours. This elevated risk is linked to chronic immunosuppression and activation of oncogenic pathways such as transforming growth factor beta and nuclear factor if activated T-cells (TGF-β and NFAT), which promote cell proliferation, immune evasion, and angiogenesis. [28]

4.4.1.7. Pharmacological interactions

CsA is a potent inhibitor of cytochrome P450 enzymes (especially CYP3A4) and transporters such as P-glycoprotein. These interactions can significantly alter the pharmacokinetics of concomitant anticancer drugs, leading to increased toxicity, drug accumulation, or reduced therapeutic efficacy. This complexity poses a challenge in combination chemotherapy regimens. [28]

4.4.2. Phytotherapy for cyclosporine toxicity

The chronic toxicity caused by CsA has motivated the search for adjuvant interventions, including the use of phytotherapeutic products, particularly within Chinese herbal medicine (CHM), with the aim of reducing the toxic profile of CsA without compromising its immunosuppressive action. [29]

A comprehensive review by Woon et al. (2024) identified multiple interactions between Chinese medicinal plants and CsA. A total of 27 studies documented specific interactions between CsA and different phytotherapeutic products, many of which focused on their ability to alter CsA bioavailability or modulate its toxicity. [29]
Based on this review, the compounds with the strongest experimental support were selected for in-depth analysis:

4.4.2.1. *Panax ginseng* (Korean Red Ginseng)

Panax ginseng is one of the most extensively studied medicinal plants It was observed that its administration in animal models significantly reduced oxidative stress and renal dysfunction induced by CsA. Furthermore, it contributed to mitigate drug-induced glucose intolerance and reduced cellular damage. These effects are attributed to its antioxidant and anti-inflammatory activity as well as its ability to preserve mitochondrial integrity. At controlled doses, ginseng did not negatively alter cyclosporine-induced immunosuppression, which underscores its potential use as a therapeutic adjunct. [29]

4.4.2.2. *Schisandra sphenanthera* and *Schisandra chinensis*

These two species, widely used in traditional Chinese medicine, have shown the ability to increase the bioavailability of CsA, thus reducing the dosage required to reach therapeutic levels. In addition, *Schisandra spp*. have demonstrated hepatoprotective, nephroprotective and neuroprotective effects in animal models treated with other immunosuppressants of similar toxicity. [29]

4.4.2.3. *Cordyceps sinensis*

This medicinal fungus has shown in preclinical studies the capacity to reduce CsA plasma concentrations, which could potentially lower its adverse effects if dose adjustments are carefully made. Although the exact mechanisms are not fully understood, interactions with intestinal transporters and metabolic enzymes are suspected. [29]

4.4.2.4. *Ginkgo biloba*

Known for its antioxidant and vasodilator effects, *Ginkgo biloba* has been studied for its interaction with CsA. A significant decrease in CsA plasma concentration was observed, which may reduce its toxicity, although with the risk of losing immunosuppressive efficacy if the dosage is not adjusted. Therefore, its use requires caution and close pharmacological supervision. [29]

4.4.2.5. *Zingiber officinale (*Gingiber) and *Glycyrrhiza uralensis* (Licorice)

Both plants were found to reduce CsA bioavailability in animal models. This effect is likely due to the induction of cytochrome P450 enzymes and P-glycoprotein transporters, accelerating CsA metabolism and clearance. While this may reduce hepatic and renal toxicity, it must be carefully controlled to avoid underdosing. [29]

In conclusion, phytotherapy offers a promising strategy to mitigate the toxic effects associated with the use of cyclosporine, especially with regard to liver, renal and metabolic protection. However, most of the studies reviewed are preclinical (primarly in animal models), and more extensive clinical research is required to validate both efficacy and safety in humans. [29]

4.5. Cyclophosphamide

Cyclophosphamide is an alkylating agent that acts as a prodrug, meaning it must be metabolizedin the body to exert its therapeutic effect. its historical role in the CMF regimen (cyclophosphamide, methotrexate, and fluorouracil) marked a significant milestone in breast cancer treatment since the 1970s. [30]
After administration, it is metabolized in the liver by the cytochrome P450 enzyme system, producing active metabolites such as phosphoramide mustard and acrolein. [30]

Phosphoramide mustard is the main alkylating agent. It forms covalent bonds with DNA, creating both interstrand and intrastrand crosslinks. These crosslinks prevent DNA replication and RNA transcription, directly interfering with the cell cycle of tumor cells. As a consequence, apoptosis or programmed cell death is induced. [30]

Because the alkylating action of cyclophosphamide is non-selective, it also affects other rapidly dividing healthy cells, such as hematopoietic, gastrointestinal, and hair follicle cells, explaining common side effects like myelosuppression, nausea, and alopecia. [30]

4.5.1. Cyclophosphamide toxicity

The use of cyclophosphamide as a chemotherapeutic agent, although effective against various types of cancer such as breast cancer, is associated with significant adverse effects on multiple organs due to its systemic toxicity. This toxicity is mainly mediated by acrolein, a metabolite generated during the hepatic metabolism of the drug, which induces oxidative stress, cellular inflammation, apoptosis and mitochondrial dysfunction. Of note, long-term adverse effects—particularly on the central nervous system—have gained more attention in recent years. [30]

4.5.1.1. Chemotherapy-induced cognitive dysfunction and neurotoxicity (CICD)

One of the most relevant findings is the association between cyclophosphamide treatment (as part of the CMF regimen) and the appearance of chemotherapy-induced cognitive dysfunction (CICD). This phenomenon, also known as *chemobrain*, involves a variety of neurological and neuropsychological deficits, such as: memory and learning difficulties, problems with attention and concentration, slowness in cognitive processing and executive function impairments. [30]

These symptoms can persist for years, or even decades, after the end of treatment. Several studies have reported that patients treated with CMF showed cognitive impairment up to 20 years after chemotherapy. [30]

The pathophysiological mechanisms that could explain this cyclophosphamide-related neurotoxicity:

- Passage of cyclophosphamide through the blood-brain barrier (BBB): Unlike other chemotherapeutics such as methotrexate, cyclophosphamide is able to cross the BBB, which allows it to directly affect the brain tissue. [30]
- Induction of neuroinflammation: Once in the central nervous system, it induces the release of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β) and interleukin 6 (IL-6), which generate a chronic inflammatory environment that is harmful to neurons. [30]

- Structural brain damage: Cyclophosphamide has been associated with the reduction of the volume of the hippocampus and the grey matter. The damage to oligodendrocytes and neuronal precursor cells, affects myelination and synaptic plasticity. [30]
- Alteration of the BBB: chronic inflammation, exacerbated by cyclophosphamide can increase BBB permeability, allowing further entry of cytokines and toxins into the brain, thereby perpetuating neuronal injury [30].

It is also important to note that many of the initial studies on CMF did not account for long-term effects, nor did they include sufficiently diverse patient samples. Cumulative toxicity—particularly in older patients or those with comorbidities—may increase the risk of cognitive impairment. Likewise, there is a need to investigate genetic and immunological factors that may predispose certain individuals to more severe toxicity, such as variations in immune response or drug metabolism. [30]

4.5.2. Phytotherapy for cyclophosphamide toxicity

Phytotherapy has emerged as a promising adjuvant strategy to mitigate cyclophosphamide side effects, due to the pharmacological potential of certain plant compounds with antioxidant, anti-inflammatory and cytoprotective properties. [31]

Several preclinical studies have demonstrated that various phytochemicals present in cereals are able to modulate intracellular signaling pathways involved in toxicity processes. One of the most relevant mechanisms is the activation of the Nrf2/ARE pathway, which triggers the endogenous production of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), contributing to counteract oxidative stress. In this context, compounds such as curcumin (from *Curcuma longa*), baicalin (*Scutellaria baicalensis*) and quercetin (found in barley, pomegranate and root), stand out for their well-documented ability to restore redox balance and protect liver, kidney, and neurological functions. [31]

Another key pathway is the inhibition of NF-κB, a central transcription factor in the inflammatory cascade. Its deregulation, enhanced by cyclophosphamide, increases the release of proinflammatory cytokines such as TNF-α, IL-1β and IL-6. Compounds such as cinnamaldehyde (from *Cinnamomum spp*.) and resveratrol (present in red root) have been shown to inhibit this pathway, thus reducing systemic inflammation and protecting tissues such as the brain, liver, urinary tract. [31]

Likewise, other phytocompounds act on complementary pathways such as MAPK/ERK and PI3K/AKT, which are involved in the regulation of apoptosis and cell survival. Together, these strategies allow a multifactorial modulation of cyclophosphamide-induced disease. Although most of the evidence comes from studies in animal models, the results justify future clinical research with the aim of integrating these interventions into personalized oncological protocols. The following table summarises the main organs vulnerable to the toxic effects of cyclophosphamide, the type of toxicity observed, natural compounds with protective potential, and their mechanisms of action. (**Table 3**)

AFFECTED ORGAN	TYPE OF TOXICITY	PROTECTIVE COMPOUND	MAIN MECHANISM OF ACTION
Liver	Hepatoxicity, oxidative stress, inflamation, cell necrosis	Curcumin Baicalin Silymarin Quercetin	Activation of Nrf2/ARE, Inhibitionof NF-*κB, supression TNF-*α i IL-6
Kydney	Nephotoxicity, glomerulonephritis, tubular damage	Quercetin Allicin Rosmarinic acid	Reduction of oxidative stress and lipid peroxidation, mitochondrial stabilization
Reproductive system	Infertility, germ cell apoptosis, hormone imbalance	Curcumin Alicin Baicalin	Prevention of mitochondrial apoptosis, hormonal regulation, reduction of ROS
Central nervous system	Cognitive dysfunction, neuroinflammation, cerebral oxidative stress	Resveratrol Curcumin Baicalin	Inhibition of NF-κB, reduction of IL-1β and TNF-α, activation of Nrf2
Lungs	Pulmonary fibrosis, alveolar inflammation	Nigella sativa extract Various flavonoids	Reduction of IL-6 and inflammatory markers, antioxidant action
Urinary tract	Hemorrhagic cystitis, epithelial damage due to acrolein	Ursolic acid Punica granatum Curcumin	Epithelial protection, detoxification of toxic metabolites, inflammatory inhibition

Table 3. Compounds that protect against cyclophosphamide-induced toxicity depending on the affected organ. [31]

4.6. Platinum compounds

Platinum-based compounds, such as cisplatin and carboplatin, are widely used chemotherapeutic agents in oncology, particularly in the treatment of various subtypes of breast cancer. Their primary mechanism of action is based on the induction of DNA damage in tumor cells, which triggers the activation of apoptosis. [32]

Once administered, these compounds enter the tumour cell mainly by passive diffusion or via specific transporters such as Copper Transporter 1 (CTR1).
Once administered, these compounds enter tumour cells primarily through passive diffusion or via specific transporters such as CTR1. Inside the cell, the acidic intracellular environment activates the pharmacophore through hydrolysis, replacing chloride ligands with water molecules. This activation allows the platinum compound to covalently bind to guanine residues in DNA. [32]

This binding results in the formation of DNA crosslinks, which can be: [32]

- Intra-strand crosslinks: Occurring within the same DNA strand, causing local distortions.
- Inter-strand crosslinks: Formed between complementary DNA strands, which prevents their separation during DNA replication or transcription.

The accumulation of such DNA damage disrupts cell cycle progression and activates the DNA damage response (DDR). In tumour cells with functional DNA repair mechanisms, these crosslinks can be efficiently repaired. However, in certain breast cancer subtypes — particularly those with homologous recombination deficiency (HRD) or BRCA1/2 mutations — the DNA repair capacity is compromised. As a result, these cells exhibit heightened sensitivity to the DNA-damaging effects of platinum compounds. [33]

4.6.1 Platinum compounds toxicity

Platinum compounds are associated with a wide range of adverse effects, some of which can be serious or even limit their therapeutic application. The toxicity induced by these drugs

affects various organs and systems, representing a clinical challenge in the planning and monitoring of cancer treatment. [34]

4.6.1.1. Nephrotoxicity

Cisplatin is particularly known for its renal toxicity. After administration, it accumulates in renal proximal tubule cells, where it induces oxidative stress, inflammation, tubular necrosis and apoptosis. This process can trigger acute renal failure, compromising glomerular and tubular function. Nephrotoxicity can be partially prevented by intensive hydration, forced diuresis and renal function monitoring, but it remains a frequent cause of treatment discontinuation in susceptible patients. [34]

4.6.1.2. Neurotoxicity

Peripheral neuropathy is another common complication, especially associated with oxaliplatin and cisplatin. It manifests as paresthesias, dysesthesias, loss of sensibility and, in more advanced cases, motor impairment. This toxicity is dose-dependent and may persist for months or years after the end of treatment. Its physiopathology is related to direct axonal damage, drug accumulation in dorsal ganglia and mitochondrial alterations. [34]

4.6.1.3. Ototoxicity

Cisplatin can induce progressive and irreversible hearing loss, especially in children and older adults. This effect is due to damage to the hair cells of the cochlea, due to ROS generated during drug exposure. Clinically, it often affects high frequencies and may go unnoticed without baseline and follow-up audiological evaluation. [34]

4.6.1.4. Myelosuppression

Carboplatin, unlike cisplatin, has less nephrotoxicity but a greater propensity to cause myelosuppression, particularly thrombocytopenia, neutropenia and anemia. This bone marrow suppression increases the risk of infections and sepsis and may require the administration of colony-stimulating factors, transfusions or modification of the therapeutic regimen. [34]

4.6.1.5. Gastrointestinal toxicity

Both cisplatin and carboplatin are highly emetogenic, causing severe nausea and vomiting in the absence of adequate prophylaxis. This effect is related to the direct stimulation of the vomiting center and the release of serotonin in the gastrointestinal tract. Although it can now be effectively managed with antiemetics such as 5-HT3 antagonists and NK-1 receptor antagonists, it continues to significantly affect patients' quality of life during treatment. [34]

4.6.1.6. Cardiotoxicity

Recently, cardiotoxicity has emerged as a significant adverse effect of platinum-based compounds, although it has traditionally been less well recognized. According to research mechanisms include oxidative stress in the myocardium, endothelial dysfunction, mitochondrial damage, and alterations in cardiac electrical. [35]
These alterations can translate into various clinical manifestations, such as:

- Myocardial ischemia or acute myocardial infarction.
- Arrhythmias (atrial fibrillation, atrioventricular block)
- Left ventricular systemic dysfunction
- Prolongation of the QT interval and risk of malignant arrhythmias.

Although the incidence is relatively low, its clinical impact can be severe, especially in patients with pre-existing cardiovascular comorbidities. For this reason, it is recommended to perform a previous cardiac assessment, as well as electrocardiographic and echocardiographic monitoring during and after treatment in high-risk patients. [35]

4.6.2. Phytotherapy for platinum toxicity

Phytotherapy—particularly traditional Chinese herbal medicine—has emerged as a promising complementary strategy to reduce toxicity and improve treatment tolerance.
According to a systematic review and meta-analysis of 17 clinical studies demonstrated that the use of Chinese herbal compounds (CHCs) as adjuvant therapy was significantly effective in reducing chemotherapy-related adverse effects, including those induced by platinum-based agents. Evidence showed a reduction in the incidence of grade III/IV neutropenia, nausea, vomiting, fatigue, and loss of appetite. Moreover, the use of CHCs was associated with an overall improvement in patients' quality of life, as assessed by validated instruments such as the EORTC QLQ-C30. The most commonly used herbal formulas included ingredients such as *Astragalus membranaceus*, *Panax ginseng, Curcuma longa*, and other adaptogenic and antioxidant plants. [36]

On the other hand, another article presents a detailed review of the molecular and pharmacological properties of various plants traditionally used in breast cancer treatment. This work highlights several bioactive compounds—such as ginsenosides from *Panax ginseng*, curcumin from *Curcuma longa*, allicin *from Allium sativum*, and lignans from flaxseed (*Linum usitatissimum*)—which possess not only antitumor activity but also immunomodulatory, antioxidant, and anti-inflammatory properties that may help mitigate chemotherapy-related adverse effects. For instance, curcumin has been shown to reduce platelet-induced oxidative stress, potentially offering protection against nephrotoxicity. Similarly, ginsenosides such as Rg3 have been linked to enhanced efficacy of cytotoxic drugs while simultaneously reducing systemic toxicity. [37]

Furthermore, several studies cited in these articles support the synergistic use of these herbal extracts alongside conventional treatments such as cisplatin and doxorubicin. Synergistic effects have been observed in the inhibition of cell proliferation, induction of apoptosis, and modulation of signaling pathways such as NF-κB, and Mitogen-Activated Protein Kinase (MAPK), suggesting that phytotherapeutic compounds may act as modulators that reduce toxicity without compromising oncological efficacy. [37]

In conclusion, phytotherapy—especially in the form of CHCs or specific extracts such as curcumin, ginseng, and garlic—shows significant potential in reducing the toxic effects of platinum-based therapies in breast cancer. While current findings are promising, they underscore the need for larger, well-controlled clinical trials to better define the optimal dosages, interactions, and safety profiles of these complementary interventions. [37]

4. DISCUSSION

The literature review conducted has identified the main adverse effects associated with chemotherapeutic agents used in breast cancer treatment. Anthracyclines, taxanes, fluorouracil, cyclophosphamide, platinum compounds, and cyclosporine exhibit toxicities that, despite originating from different pathophysiological mechanisms, converge on common pathways such as oxidative stress, systemic inflammation, and mitochondrial dysfunction.
Overall, there is broad agreement across the reviewed studies regarding the underlying mechanisms of toxicity. However, discrepancies remain concerning the clinical relevance of certain adverse effects. For instance, the utility of fluorouracil has been questioned in studies like GIM2, which report no significant survival benefit when it is added to contemporary therapeutic regimens.

Of particular interest are recent methodological innovations, such as the use of cardiomyocytes derived from induced pluripotent stem cells (hiPSC-CM) to predict anthracycline-induced cardiotoxicity, and pharmacogenetic studies identifying polymorphisms linked to taxane-related neurotoxicity. Additionally, the exploration of phytotherapy as an adjuvant strategy—particularly with extracts like *Platycodongrandiflorum*, *Hibiscus rosa-sinensis*, β-elemene, and curcumin—represents a promising translational research direction.
The findings confirm that chemotherapy-related toxicity not only hampers treatment continuity but can also severely affect patients' quality of life and, in some cases, their survival. These results validate the initial hypothesis: understanding the toxicological profiles of chemotherapeutic agents is crucial for developing effective mitigation strategies. In this regard, combining chemotherapeutic agents with natural compounds capable of modulating toxicity pathways emerges as a relevant approach. Studies demonstrating synergy—such as between fluorouracil and β-elemene, or between paclitaxel and *Hibiscus rosa-sinensis* extract—suggest that chemotherapy doses may be reduced without compromising efficacy, thereby minimising adverse effects.

One of the key contributions of this review lies in the critical integration of identified toxicity mechanisms with phytotherapeutic strategies, bridging two fields often considered separately. This correlation offers a more functional and translational perspective, opening new lines of intervention grounded in preclinical evidence.
Furthermore, the continued widespread use of drugs such as fluorouracil—despite a lack of clear benefit in specific clinical contexts—warrants critical reassessment of established therapeutic protocols in light of emerging data.

As a literature review, this study has inherent methodological limitations: restricted article selection, possible publication bias, and limited clinical data on the safety and efficacy of phytotherapeutic compounds. Much of the available evidence comes from preclinical models, complicating direct extrapolation to human patients. Moreover, significant heterogeneity in study design, population characteristics, and evaluation criteria limits comparability and external validity.

Nonetheless, the clinical implications are clear. First, they underscore the need for rigorous monitoring of drug-specific toxicities, particularly in patients with predisposing risk factors. Second, they highlight the potential of phytotherapy as a complementary strategy capable of reducing toxicity and improving tolerability without impairing therapeutic outcomes. hiPSC-CM and pharmacogenetics into clinical practice may help usher in a more predictive and individualised approach to care. Likewise, clinical validation of natural antitoxic compounds could broaden the therapeutic landscape in breast cancer treatment.

Future efforts should prioritise controlled, randomised clinical trials to validate the protective effects of phytotherapeutic agents in humans and to explore potential pharmacokinetic

interactions with standard treatments. On a translational level, improving the bioavailability and standardisation of natural formulations is essential.

Finally, advancing toward personalised therapeutic protocols based on genetic and epigenetic biomarkers will enable prediction of individual susceptibility to drug toxicity. When combined with natural adjunctive therapies, this approach may significantly improve both the efficacy and tolerability of chemotherapy in breast cancer patients.

5. CONCLUSIONS

The toxicity associated with chemotherapy for breast cancer remains a significant clinical challenge, affecting not only treatment tolerance but also patients' quality of life and, in some cases, survival. Despite considerable progress in oncological efficacy, the systemic impact of these drugs is substantial, often involving multi-organ toxicities and long-term sequelae that persist beyond the treatment phase.

Therapeutic strategies must move beyond standardisation to address the biological and clinical heterogeneity of patients. Personalising treatment is not merely a desirable option—it is both a clinical imperative and an ethical responsibility. The integration of predictive models, pharmacogenetic tools, and complementary approaches—such as the evidence-based use of natural compounds with protective effects—paves the way toward a more effective, safer, and more compassionate form of oncology.

The evidence reviewed indicates that specific phytotherapeutic interventions may significantly reduce chemotherapy-induced adverse effects, promote greater treatment adherence, and minimise medium- and long-term complications. However, their incorporation into clinical practice requires rigorous validation through controlled trials and appropriate regulation of phytotherapeutic products.

Ultimately, we must advance toward a model of personalised medicine that takes into account not only the tumour's molecular profile but also each patient's tolerance thresholds, environment, preferences, and individual risk factors. Only through this approach can we deliver truly patient-centred care that balances curative intent with overall well-being.

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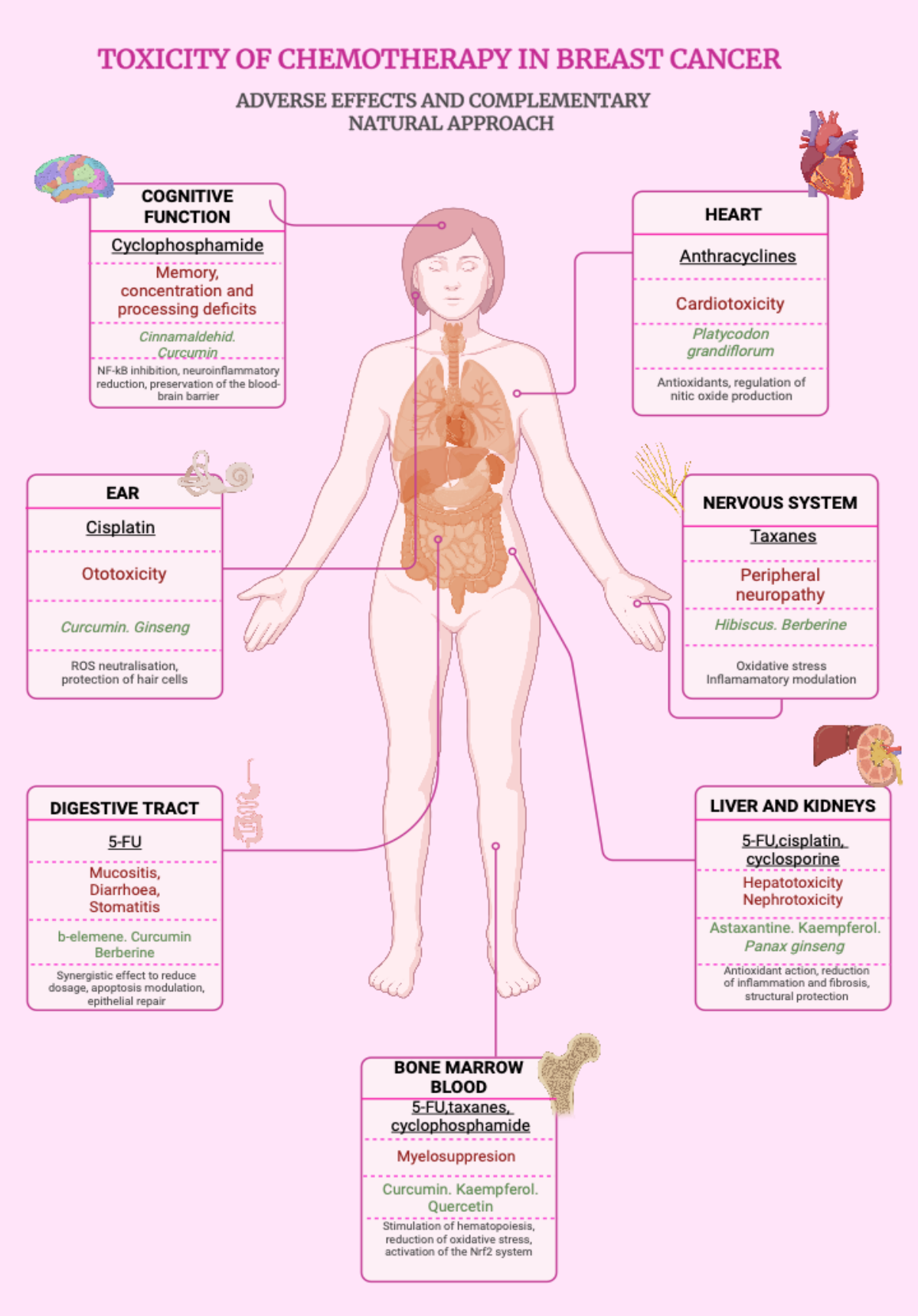
7. ANNEX



Annex 1: Infographic on the side effects of chemotherapy on different organs and how natural approaches can help mitigate them.