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SYNERGISTIC ONCOLOGY: HOW CHEMOTHERAPY EFFECTS CAN BE REDUCED BY USING HERBAL MEDICINE

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Abstract

Cancer is one of the problems we really do need to keep researching to find an actual cure. For years now, chemotherapy has been used as a go-to treatment option. But it comes up with several side effects. Some of these side effects are nausea and vomiting, mouth sores, nerve damage and fatigue. These side effects can be so bad that people have to stop treatment or take doses, which is not good for getting rid of the cancer. The things we are doing now to help people with these side effects are not working well. Using medicine that is based on evidence might help reduce these side effects without making the chemotherapy less effective. This review looks at all the research on medicines that can help with specific side effects like nausea and vomiting, mouth sores, nerve damage and fatigue. Most people tolerate them well, and they do not have a lot of serious side effects. Astragalus, in particular, is really helpful for those who are going through chemotherapy. It supports recuperation. Green tea and curcumin, as well, can help when the problem is nerve-related. They can also feel less worried overall. In a broad sort of way, astragalus, tea blends, curcumin, and other similar supplements might help a bit because they can support the body during treatments like chemotherapy. If someone decides on herbal remedies and they come from reliable sources, then, in most cases, they can be used alongside chemotherapy more safely. Choosing supplements that are based on evidence may lower some chemo side effects, and it can make treatment easier to stick with. Doctors and patients really should coordinate, just to make sure herbal medicine is used safely and in a way that actually helps. Herbal medicine can be one more route to support people with cancer, helping them get the treatment they need without as many unpleasant effects.

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INTRODUCTION

Cancer is one of the problems we really do need to keep researching to find an actual cure. For years now, chemotherapy has been used as a go-to treatment option. Usually, it is paired with surgery, radiation, or another form of care, depending on the whole situation. Each year, a lot of patients go through chemotherapy for several kinds of cancer, like breast, lung, colorectal, ovarian and blood cancers, just to name a few. Chemotherapy basically works by aiming at cells that divide quickly and are rapidly dividing. Still, it can also damage normal cells that divide rapidly, for example, the ones in the bone marrow, the lining of the gut, and even hair follicles.

Since more individuals are getting treated and living longer after cancer, these unwanted effects have become more noticeable in care and even in the final results. Chemotherapy can create side effects both in the short term and the long run. A lot of research studies from databases, including PubMed, Cochrane Library and Google Scholar, are reviewed, and studies that were of good quality, relevant to cancer patients and had good evidence are chosen. By organising the information by the type of effect and the herb being used. Also looked at how the herbs worked, if they were safe and what the outcomes were.

1.1 Background of the Study

In this century, cancer is one of the most concerning topics in the world. By checking the figures given by the World Health Organisation (WHO), it is an alarming situation. There are millions of deaths per year, and new cases are added daily. By analysing the numbers estimated by WHO, it is inevitable that by 2040, the number will go up to 28 million cases per year. This catastrophic condition is due to several reasons, e.g., tobacco, obesity, and a sedentary lifestyle (Sung et al., 2021). It is most common in developing countries because of fewer resources for early detection and a low rate of therapeutic facilities.

For this deadly disease, if we check the cure, there is only one option, which comes at a high price. That is chemotherapy, which has shown severe side effects, e.g.,

1. Gastrointestinal Toxicity
2. Hematological Toxicity
3. Peripheral Neuropathy
4. Heptotoxicity
5. Nephrotoxicity
6. Cardiotoxicity
7. Fatigue
8. Cognitive Impairment
9. Immune Dysfunction

Along with chemotherapy, cytotoxic drugs are prescribed. These drugs are used in different types of malignancies, i.e., breast, lung or blood-related cancers. They include;

- Cisplatin
- Doxorubicin
- Paclitaxel
- Cyclophosphamide
- 5-fluorouracil

They improve the patient situation but at the price of low quality of life and maybe discontinuation of treatment (Viale, 2020).

1.2 Overview of Adverse Effects

➔ Gastrointestinal toxicity involves nausea, vomiting, diarrhoea, and oral mucositis.

➔ Peripheral neuropathy includes numbness, tingling and pain in the limbs.

➔ Haematological toxicities: myelosuppression, neutropenia, anaemia and thrombocytopenia.

➔ Cisplatin is known for its nephrotoxic and ototoxic effects.

➔ Anthracyclines bring cardiotoxicity risk.

➔ Methotrexate, with ifosfamide, causes hepatotoxicity.

Besides these physical effects, patients also experience fatigue, cognitive impairment, immune disruption and psychological issues, making it harder for patients to tolerate all these together (Seretny et al., 2014).

1.3 Limitations

To counter the toxicities induced by chemotherapy, modern oncology has made progress, e.g., with antiemetics, haematopoietic

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growth factors, and nephroprotective agents. Although it helps with the outcome, it is expensive, which makes it difficult for every patient to afford. There is no prevention of this deadly disease, just a treatment which is based on symptoms. Antiemetics show temporary results, meaning patients can get nausea and vomiting later on (Horneber et al., 2012).

Integrativeoncology is the emerging discipline trying to reduce chemotherapy-induced effects and, along with that, making efforts to improve the quality of patients' lives. Its focus is to reduce toxicities, boost the immune system and improve the anticancer therapy results. Multiple centres in the world have tried to set up integrative medicine programmes, which shows that nowadays people are more inclined towards herbal medicine. The centres are

1. Memorial Sloan Kettering Cancer Centre,
2. MD Anderson Cancer Centre, etc.

Moreover, guidelines have been released by the Society for Integrative Oncology (SIO) that support certain complementary interventions, e.g., acupuncture, and natural health products to counter the symptoms caused by chemotherapy (Lyman et al., 2018).

In the complementary interventions, herbal medicine sits in the centre and plays a pivotal role. It is recorded to be the most used modality by cancer patients because

- It is easy to obtain.
- People are familiar with it.
- And people feel safe while using it because it is something which naturally occurs.

1.4 Herbal Medicine Role in Oncology

It is not new to use herbal medicine as a supplement. It has been used for the treatment and mitigation of various diseases since the beginning of the world. Traditional systems of medicine include the following:

1. Ayurveda,
2. Traditional Chinese Medicine (TCM),
3. Unani, and
4. African plus South American healing traditions

These systems used herbal formulations for different types of health issues. Some of the most potent chemotherapeutic agents obtained from plants have shown that the herbal medicine has a particular place in integrative oncology (Newman & Cragg, 2020). It includes;

- vincristine and vinblastine (Vinca rosea),
- paclitaxel (Taxus brevifolia),
- camptothecin analogues (Camptotheca acuminata), and
- etoposide (Podophyllum peltatum)

The herbal drugs or products sound useful because they act as antioxidants, anti-inflammatories, immunomodulators, hepatoprotectors, neuroprotectors and anticancer agents. For example, curcumin (Curcuma longa), epigallocatechin-3-gallate (EGCG) (green tea), ginsenosides (Panax ginseng), silymarin (Silybum marianum), and withanolides (Withania somnifera). These phytochemical agents act with standard chemotherapeutic agents and boost the efficacy of treatment while reducing the harmful effects.

1.5 Objectives

Although there is much research that has been done on using herbal medicine with chemotherapy. But evidence is lacking in this domain, with heterogeneity in study designs and the dosages of herbal preparations. Spontaneously, safety concerns arose, particularly the role of herbal drugs via changes in cytochrome P450 enzyme pathways.

This review is designed to analyse the preclinical and clinical evidence on herbal medicine for reducing chemo-adverse effects. Its major focus is on protective action, its safety, tolerance and how beneficial it will be to use herbal medicine in real practice. In synergistic oncology, we used herbal medicine with standard chemo as a complementary way. This review will offer complete evidence-based guidance for those who are trying to manage cancer treatment toxicity, e.g., clinicians, researchers, and patients.

The review aims towards standard, safer, and more effective practices in which we

- discuss the gaps that exist in the literature,

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- will give you a direction for future research

If herbal treatments can safely help lower chemotherapy side effects, then patients can be helped in a whole bunch of ways. Patients will be able to manage chemotherapy better; they can stick with the course for a while and not bounce around. They will also keep their condition steady and stay physically strong, and, yes, they will have a life, not just another medical schedule.

OVERVIEW OF CHEMOTHERAPY GROUPS AND HOW THEY SHOW TOXICITY

Chemotherapy drugs are divided into groups based on different factors:

- What role will they play in the body, for example, the mechanism of action?
- Their Chemical Composition and Properties

When we can figure out how each group is affecting the cancerous and normal cells, it will give us a clear picture of the specific effects that will be shown by using a specific group of drugs. It helps us to plan supportive measures effectively.

2.1 Alkylating Agents

These are the oldest group of chemo drugs. Their origin came from nitrogen mustard compounds that were used in the 1940s. They work by directly approaching the DNA, making them forcefully cross-linked between DNA strands. The cross-link will block DNA replication and transcription. It eventually stops the cancer cells from going into apoptosis. Some of the alkylating agents are

- cyclophosphamide,
- chlorambucil,
- melphalan,
- busulfan, and
- procarbazine, etc.

In clinical work, these agents cause major side effects, including myelosuppression and gastrointestinal effects. The myelosuppression causes harm to the bone marrow, especially to the WBCs. Its harm is dose-dependent. The common gastrointestinal effects are nausea, vomiting, and mucositis.

2.2 Platinum Compounds

The list of widely used platinum compounds is cisplatin, carboplatin and oxaliplatin. Their way of working is similar to alkalising agents. The difference is that it directly catches the guanine base in DNA. These compounds cause neurotoxicity, which eventually causes peripheral neuropathy or CIPN in 30-100% of patients. It depends on the exact compound and dosage.

With cisplatin, the risk is highest. A dose over 400 mg/m^2 can cause nerve damage permanently. Oxaliplatin triggers acute neuropathy, and its chances are about 90%. And once either kind of neuropathy shows up, the cumulative and the acute patterns are generally not reversible either. On top of the nerve issues, platinum therapy can also cause nephrotoxicity, ototoxicity (hearing impairment), nausea and vomiting, and even myelosuppression, which can genuinely restrict how well the bone marrow rebounds.

2.3 Antimetabolites

It can lead to gastrointestinal toxicity, oral mucositis, diarrhoea, and nausea. When it is given in a higher dose, it can trigger kidney problems and hepatotoxicity. For example, when 5-FU is given as a continuous infusion, it often ends up causing worse diarrhoea and hand-foot syndrome, while bolus dosing seems more tied to myelosuppression and mucositis, not the other way around. Hand-foot syndrome, sometimes phrased as palmoplantar erythrodysesthesia, is usually characterised by really intense redness, plus blistering, and aching pain in the palms and soles.

2.4 Taxanes and Vinca Alkaloids

In general, these agents work through microtubule disruption. Together, these mechanisms end up interfering with cell division during mitosis. Taxanes are a big reason for chemotherapy-induced peripheral neuropathy. With paclitaxel, CIPN shows up in about 30-75%

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of patients, especially when the cumulative doses go past 300 mg/m².[4] This neuropathy seems dose-dependent, and in most cases it can be reversed if it is caught early, and then the therapy is halted. On top of that, taxanes may trigger severe hypersensitivity reactions; those are usually managed with premedication beforehand. They also tend to cause myalgia/arthralgia, meaning muscle and joint pain, and they can lead to myelosuppression. Vinca alkaloids cause CIPN less often than taxanes, but they're more inclined toward motor neuropathy. Vincristine leads to constipation in up to 80% of patients.

MAJOR CATEGORIES OF CHEMOTHERAPY-INDUCED ADVERSE EFFECTS

3.1 Gastrointestinal Toxicity

In the brain, there is an area called the chemoreceptor trigger zone that is like a listener for signals that can make people feel sick. At the time, the stomach and intestines can get upset when they are damaged by the chemotherapy. Then some chemicals in the body, like serotonin and substance P, help turn on the part of the brain that makes people vomit. They work together to make the whole thing happen with chemotherapy-induced nausea and vomiting, or CINV. Acute nausea or vomiting shows up within 24 hours after the chemotherapy dose is given, while delayed CINV tends to start after 24 hours and may last for days.

The capacity of a drug to cause vomiting is different; some are notorious. For example, those agents which contain cisplatin, cyclophosphamide, or dacarbazine are likely to cause CINV in 90% of patients (Hesketh et al., 2017). Its pathophysiology is the activation of chemoreceptors and then the release of neurotransmitters, e.g., serotonin (5-HT_3), substance P, dopamine, etc.

Oral mucositis is the ulceration and irritation of the oral mucosa and the gut lining. Its chance to occur is 40% in patients on standard therapy and upto 80% in high-dose patients (Lalla et al., 2014). In clinical terms, mucositis appears as sore oral ulceration, dysphagia, reduced ability to eat, and systemic infections. It is because the mucosal barrier is basically disrupted. In the worst conditions, it leads to the discontinuation of chemotherapy, solely relying on the parental nutrition and the patient being admitted to the hospital. It overall affects the treatment outcome.

3.2 Haematological Toxicity

It is the side effect that comes up with cytotoxic therapy. The bone marrow divides the progenitor cells. The result is myelosuppression. It is the suppression of haematopoiesis that results in neutropenia, anaemia, and thrombocytopenia.

Neutropenia is when the neutrophil count drops below 1.5×10^9/L. It is the most significant haematological complication. It raises the risk of bacterial and fungal infection. The other one is febrile neutropenia. It is the fever occurring along with severe neutropenia. It is a medical emergency condition and has a high mortality and morbidity rate. The drugs associated with severe myelosuppression are anthracyclines, alkylating agents, topoisomerase inhibitors, and platinum-based compounds.

Anaemia is driven by the suppression of erythropoiesis. It can cause fatigue, reduce capacity for exercise, impair cognitive function, and result in an overall worse quality of life. The underlying causes include cytotoxic direct effects on erythroid progenitors, decreased renal production of erythropoietin, and iron sequestration.

Thrombocytopenia arises from megakaryocyte suppression. It can cause spontaneous bleeding, especially if the platelet count goes under 20×10^9/L.

So, the total haematological load from chemotherapy is the biggest driver of how the treatment ends up and the overall outlook of the patient.

3.3 Peripheral Neuropathy

It can be shortened as CIPN, and the major issue that can result in treatment discontinuation. It occurs because chemotherapeutic agents cause toxic effects on peripheral sensory, motor, and autonomic nerve fibres. The groups of drugs that are associated are the taxane group, platinum

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compounds, vinca alkaloids, and proteasome inhibitors. It is seen in 19-85% of patients who receive neurotoxic therapy. The severe form, which is around 30%, reported that the patient was treated with cisplatin or paclitaxel (Seretny et al., 2014).

CIPN is not just caused by a single mechanism; it is more likely to have a connection of pathways, and also the agent that is being used. For example, **platinum compounds** accumulate in the dorsal root of ganglion neurones. There, it triggers mitochondrial dysfunction, oxidative DNA harm, and apoptosis. The other one, **taxanes,** interferes with microtubule dynamics. The microtubule dynamics are needed for axonal transport, but when taxanes interfere with it, proteins and organelles struggle to move to the far distal axon, which results in axonal degeneration. The next one is **vinca alkaloids;** they interfere with the microtubule polymerisation, resulting in the weakening of the axonal upkeep. Even with a lot of research, no single pharmacological agent has been found that can prevent CIPN. So, the treatment is symptomatic and supportive care (Staff et al., 2017).

3.4 Hepatotoxicity

The liver is the main organ. It is responsible for drug metabolism. The chemo-induced hepatotoxicity includes hepatic cell injury from mild to severe, hepatic sinusoidal obstruction syndrome, drug-induced cholestasis, and fulminant hepatic failure. The agents responsible for the hepatotoxicity are methotrexate, which eventually leads to hepatic fibrosis and even cirrhosis; busulfan; and antimetabolites. There is also seen the transient hepatotoxicity, which is basically the increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). In most cases, it results in the adjustment of the dose or a pause in therapy (Grigorian & O'Brien, 2014).

3.5 Nephrotoxicity

The kidney is the main organ that is responsible for excretion. Nephrotoxicity is the problem that comes from **cisplatin**. It can cause proximal tubular injury, afferent arteriolar vasoconstriction, and oxidative damage. It targets the renal tubular epithelial cells and ends up decreasing the glomerular filtration rate. In the worst-case scenario, it can lead to acute kidney damage that needs dialysis.

The other one is **ifosfamide;** it is linked to Fanconi syndrome and haemorrhagic cystitis. And the **methotrexate triggers** nephropathy, mainly because of tubular precipitation. The effects are beyond renal impairment. Prevention of nephrotoxicity includes the usage of normal saline, magnesium supplementation, and amifostine as a cytoprotective measure before using cisplatin. It will lessen the risk (Miller et al., 2010).

3.6 Cardiotoxicity

Chemotherapy-induced cardiotoxicities are left ventricular impairment, cardiomyopathy, congestive heart failure, arrhythmias and acute coronary syndrome. It is one of the most severe setbacks from cancer therapy and a major cause of death among survivors. The treatment group for the cardiotoxicity is anthracyclines (doxorubicin, epirubicin and idarubicin). They cause cardiomyopathy, cardiomyocyte damage, topoisomerase IIβ inhibition, mitochondrial dysfunction, and apoptosis in cardiac muscle cells. The chances of anthracycline-induced cardiomyopathy increase if the cumulative doxorubicin dose passes about 400–550 mg/m^2. It leads to cardiac failure, which is irreversible (Zamorano et al., 2016).

Other than anthracyclines, another drug is cyclophosphamide. With its high dose, it leads to haemorrhagic myocarditis. Fluoropyrimidines (5-fluorouracil and capecitabine) are linked with coronary vasospasm and acute coronary failure. Bevacizumab and the other anti-angiogenic agents cause hypertension and arterial thromboembolism. For clinical monitoring, cardiotoxicity is the problem that needs to be monitored again and again. By using echocardiography, track the left ventricular ejection fraction. If any dysfunction appears, then the dose must be reduced or the treatment must be discontinued on the spot.

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For prevention, cardioprotective strategies such as dexrazoxane, an iron chelator, and liposomal doxorubicin formulations are found to enhance cardiac safety. Also, before and during therapy, analysing cardiovascular risk factors is to be a part of preventive practices.

3.7 Fatigue

Cancer-related fatigue (CRF) is the most distressing symptom that patients have to bear with. It shows up in about 70 - 100% of the patients using chemotherapy as the treatment option. It can continue appearing even after the treatment ends (Bower, 2014). It is different from the typical fatigue that a healthy person feels. It doesn't get better with rest and affects the quality of life. The underlying causes are anaemia induced by chemotherapy, hypothalamic-pituitary-adrenal axis dysregulation, inflammatory cytokines, especially IL-6, IL-1β and TNF-α, mitochondrial issues, autonomic nervous system imbalance, and circadian rhythm disruption. Managing the CRF is a major problem because medications are not effective.

3.8 Cognitive Impairment

It has a nickname, 'chemobrain' or 'chemofog', and is formally called the 'cancer-related cognitive impairment' (CRCI). It is the long-lasting effect of chemo. It has trouble with memory, attention, processing speed and executive functioning (Janelsins et al., 2014). The mechanisms of cognitive impairment are direct neurotoxicity, neuroinflammation, and oxidative stress. For example, genetic polymorphism, which is involved in drug metabolism and DNA repair, can make patients susceptible to the cognitive downswing in the first place.

3.9 Immune Dysfunction

It makes the treatment or management of cancer more complicated. For example, direct cytotoxicity of the lymphoid progenitor cells leads to numerical and functional shortcomings in T-lymphocyte, B-lymphocyte, and natural killer (NK) cells. So, the immune response becomes weak. Immunosuppression increases the risk of bacterial, viral and fungal infections. It also weakens the immune response against tumour cells. Chemotherapy-induced dysbiosis interferes with mucosal immunity and results in systemic immune imbalance. This can lead to gastrointestinal toxicity and immune dysfunction (Routy et al., 2018).

KEY HERBAL AGENTS: EVIDENCE REVIEW

4.1 Curcumin (Curcuma longa): Anti-Inflammatory and Cytoprotective Effects

Curcumin is extracted from the rhizome of Curcuma longa (turmeric). It is the most extensively used phytochemical in biomedical research. It has gained attention because of its capacity to modulate multiple molecular targets. The targets include tumour biology and chemotherapy-induced tissue toxicity, giving it a central place in synergistic oncology. The cytoprotective activity of curcumin has been found in a wide range of preclinical systems. In doxorubicin-induced cardiotoxicity, by reducing the levels of malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), decreasing the chances of cardiomyocyte apoptosis, and preserving the left ventricular ejection fraction, curcumin significantly reduces myocardial oxidative stress (Sadzuka et al., 2000).

The cardioprotective effects of curcumin are due to its iron-chelating properties. It interrupts the reactions responsible for hydroxyl radical generation in anthracycline cardiotoxicity. Also interferes with its capacity to activate Nrf2-ARE within cardiomyocytes. Curcumin has shown nephroprotective activity in in vivo studies. The mechanism is the suppression of NF-κB-mediated renal inflammatory cytokine expression, the attenuation of cisplatin-induced mitochondrial dysfunction and the restoration of depleted renal glutathione stores. For peripheral neuropathy, curcumin reduced markers of mechanical allodynia and thermal hyperalgesia. And decreasing the apoptosis of dorsal root ganglion neurones and suppressing spinal cord neuroinflammatory cytokine expression (Han et al., 2012).

In the clinical domain, curcumin has been constrained due to its aqueous solubility, high

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intestinal metabolism and low systemic bioavailability in oral formulations. A controlled trial that was conducted in 2013 by Ryan et al. demonstrated that, during chemotherapy, oral curcumin supplementation at 6 g/day was tolerated. It also reduced the inflammatory cytokine burden. Now, trials on a large scale are needed, with a standard formulation to establish definitive clinical efficacy.

4.2 Ginger (Zingiber officinale): Antiemetic Properties

Ginger, the rhizome of Zingiber officinale, has a distinguished position among herbal antiemetic agents. It has a history of use in nausea management for over 2,000 years. In the contemporary base, ginger has become the most investigated herbal product for the management of CINV. The bioactive constituents of ginger responsible for antiemetic activity are 6-gingerol and the shogaols. These compounds exert antiemetic effects through different mechanisms: **antagonism of serotonin 5-HT_3 receptors,** which are the primary target of standard ondansetron-class antiemetics; and **antagonism of substance P at NK1 receptors,** the target of aprepitant-class antiemetics (Pertz et al., 2011).

The clinical evidence for the efficacy of ginger in CINV is substantial. A trial was conducted by Ryan et al. (2012) in which ginger was administered at doses of 0.5 g and 1.0 g per day for six days. In the first three days, before chemotherapy, it significantly reduced the severity of acute nausea. It showed the most pronounced benefit in patients receiving highly emetogenic platinum-based compounds. A systematic review and meta-analysis was done by Marx et al. (2017) and concluded that ginger supplementation produced significant reductions in CINV severity. It also shows a particularly consistent benefit for acute nausea.

Beyond antiemesis, ginger demonstrates other properties, e.g., anti-inflammatory, antioxidant, and gastrointestinal mucoprotective. It also includes COX-2 inhibition, NF-κB suppression, and upregulation of mucin secretion. It also helps in the reduction of chemotherapy-induced oral and gastrointestinal mucositis. Ginger is beneficial in the recommended doses, but patients may have mild gastrointestinal discomfort.

4.3 Ginseng (Panax ginseng): Fatigue and Immune Support

Panax ginseng has been given importance due to its adaptogenic, immunostimulatory, and anti-fatigue properties. Each of which is directly related to the management of chemotherapy-associated systemic burden. The bioactive constituents of Panax ginseng are ginsenosides, a class of triterpenoid saponins.

Cancer-related fatigue is a complaint by patients who are receiving chemotherapy. The evidence for ginseng as a fatigue-modifying intervention has strengthened over the past 2 decades. A trial conducted by Barton et al. (2013), the North Central Cancer Treatment Group (NCCTG) at Mayo Clinic, demonstrated that the dose of Wisconsin ginseng (Panax quinquefolius) at 2,000 mg/day for eight weeks showed significant improvements. The scores are measured by the Multi-dimensional Fatigue Symptom Inventory (MFSI-SF). The mechanism includes the modulation of the HPA axis stress response and attenuation of cytokine-driven fatigue. It also helps in the improvement of mitochondrial bioenergetics and ATP synthesis in skeletal muscle through activation of AMP-activated protein kinase (AMPK).

Ginsenosides Rg1 and Rb1 have been demonstrated to restore lymphocyte proliferative capacity, augment NK cell cytotoxicity, enhance macrophage phagocytosis, and stimulate dendritic cell maturation in patients receiving chemotherapy. A systematic review was conducted by Jin et al. (2016), examining ginseng-treated patients who showed improvements in quality-of-life scores and reductions in gastrointestinal adverse effects as compared to chemotherapy-alone controls. Ginsenoside Rg3, extracted from red ginseng, acts as an immunostimulatory agent in clinical trials of patients receiving platinum-based chemotherapy. It shows significant improvement in immune function and treatment response rates (Liu et al., 2009).

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4.4 Milk Thistle (Silybum marianum): Hepatoprotection

Silybum marianum is known as milk thistle. Its seed extract is silymarin, which consists of silibinin, silychristin, silydianin, and isosilybin. It represents the herbal hepatoprotective intervention in the most extensively studied and clinically validated way in both conventional and integrative medicine. The hepatoprotective action of silymarin is well grounded. The preclinical evidence for silymarin's hepatoprotective activity against chemotherapy-induced liver injury is comprehensive. Silymarin administration helps in the elevation of the serum hepatic enzymes and reduces hepatic MDA concentrations. It also restored hepatic GSH content and preserved normal hepatic histological architecture. These effects are combined with its antioxidant, anti-inflammatory, membrane-stabilising, and hepatocyte-regenerative mechanisms (Abenavoli et al., 2010).

The active constituent of silymarin is silybin. It shows direct inhibitory effects on organic anion transporting polypeptide (OATP) transporters. They are responsible for the hepatic uptake of certain chemotherapeutic substrates. It suggests a cytoprotective mechanism that reduces intrahepatic accumulation of toxic drug metabolites.

In the clinical term, a trial was conducted by Ladas et al. (2010) in paediatric patients. These patients are suffering from acute lymphoblastic leukaemia (ALL) and are receiving chemotherapy. Oral silymarin administered at a dose of 5.1 mg/kg/day for 28 days produces significant reductions in AST and ALT levels. Another trial was done by Fallahi et al. (2020) and demonstrated that silymarin reduced the incidence and severity of hepatotoxicity in adult patients. It may represent more effective results in future investigations.

4.5 Ashwagandha (Withania somnifera): Neuroprotection and Stress Modulation

Withania somnifera is known as Ashwagandha. Its meaning is "smell of horse" in Sanskrit. It is used to enhance physical and cognitive endurance, minimise stress-related pathology, and boost immune resilience. Its bioactive constituents are withanolides, alkaloids, saponins, and iron-containing compounds. Withaferin A and withanolide D demonstrate the anti-inflammatory, antioxidant, anti-apoptotic, and neuroprotective activities.

In chemotherapy-induced peripheral neuropathy, Withania somnifera root extract shows significant neuroprotective activity. Its extract significantly reduces allodynia, thermal hyperalgesia and apoptosis of dorsal root ganglion neurones. The adaptogenic properties of ashwagandha are important for the management of chemotherapy-associated psychological stress and cancer-related fatigue. To examine the effects of ashwagandha root extract, a controlled trial was conducted by Biswal et al. (2013). A dose of 2,000 mg/day was given for fatigue. Its anti-fatigue and adaptogenic effects are required for the normalisation of cortisol hypersecretion. Its capacity to reverse chemotherapy-induced myelosuppression and restore bone marrow positions it as a multidimensional herbal adjunct.

4.6 Green Tea Extract (EGCG): Antioxidant Effects

The active constituents of green tea (Camellia sinensis) are catechin polyphenols. It is the most studied antioxidant in biomedical research. It is characterised by its properties, including antioxidant, anti-inflammatory, pro-apoptotic in tumour cells, and cytoprotective in normal cells. Its antioxidant action is useful due to its potency. In terms of cardiotoxicity, it has demonstrated significant cardioprotective activity. It helps in suppressing myocardial MDA elevation, sustaining cardiac GSH/GSSG ratios, reducing cardiomyocyte apoptosis, and maintaining left ventricular contractile function.

Its capacity to regulate multidrug resistance shows its potential clinical value. A trial was done by giving orally administered green tea extract. A dose up to 800 mg EGCG per day was provided, and it was safe and well-tolerated in cancer patients (Chow et al., 2005). If it is used in higher doses, it may lead to hepatotoxicity. It is important to note that the necessity of an appropriate dose is mandatory in clinical settings.

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4.7 Astragalus (Astragalus membranaceus): Immunomodulation

It is one of the most prescribed herbal medicines. It has primary therapeutic indications, e.g., it is an immune tonic and adaptogen. Its bioactive constituents include astragalus polysaccharides, astragalosides, flavonoids, and saponins. Each contributes to immunomodulatory and cytoprotective action. Evidence for its immunomodulatory action as an alternative to chemotherapy comes from trials conducted at different research institutions. A review by McCulloch et al. (2006) demonstrated that astragalus formulations produced significant improvement in survival rate, tumour response rate, and performance status. The result was that patients showed high $CD4^+$ T-lymphocyte counts, improved $CD4^+/CD8^+$ ratios, and enhanced NK cell activity.

Astragaloside IV has specifically stimulated the telomerase reverse transcriptase (hTERT) enzyme in immune cells. It leads to an increase in the lifespan of lymphocytes, which are rapidly depleted by chemotherapy. It acts by a mechanism that is selective for immune cells rather than malignant cells. It is because tumour cells exhibit telomerase overexpression that is not affected by astragaloside supplementation (Harley et al., 2011). The haematopoietic protective effects of APS are the promotion of bone marrow recovery and direct proliferative effects on haematopoietic progenitor cells. It supports the clinical settings of Astragalus as a support system for the comprehensive immune response.

Other Promising Candidates

4.8 Nigella sativa (Black Seed)

The bioactive constituent of Nigella sativa is thymoquinone. It has a wide range of cytoprotective activities. Studies have shown its capacity to reduce the risk of cisplatin-induced nephrotoxicity, doxorubicin-induced cardiotoxicity, and methotrexate-induced hepatotoxicity by its combined effects of antioxidant, anti-inflammatory, and anti-apoptotic mechanisms (Gali-Muhtasib et al., 2006). Other than its cytoprotective activities, it demonstrates direct pro-apoptotic and anti-proliferative activity in multiple tumour cell lines, e.g., in breast, lung, colon, pancreatic, and haematological malignancies. It is done by the suppression of NF-κB, PI3K/Akt, and Wnt/β-catenin signalling pathways. It showed dual effects; one is to protect normal tissues as well as to boost the anti-tumour activity of co-administered chemotherapy. To check its safety and tolerance, a study was conducted in which an oral dose of 2 g/day was given. It was safe and reduced the chemotherapy-induced nephrotoxicity (Bamosa et al., 2010).

4.9 Boswellia serrata (Indian Frankincense)

Its most potent constituent in Boswellic acids is acetyl-11-keto-β-boswellic acid (AKBA). It has shown primarily anti-inflammatory effects through selective and exclusive inhibition of 5-lipoxygenase (5-LOX), which is combined with NF-κB inhibitory activity. Boswellia preparations have been studied as a neuroprotective and analgesic alternative. It was done by a trial conducted by Sury et al. (2011), which shows that Boswellia extract significantly reduced the chances of cerebral oedema. For neuropathic pain, Boswellia's LTB_4 and PGE_2 suppressive activities exert an analgesic effect. But the clinical trial in CIPN is limited and needs to be prioritised in future research.

4.10 Panax notoginseng and Compound Danshen (Dan Shen)

The principal constituent of Salvia miltiorrhiza (Danshen) is Tanshinone IIA. It showed significant cardioprotective activity against doxorubicin-induced cardiomyopathy. It minimises myocardial apoptosis through the Sirt1/p53 pathway modulation. It also reduces the inflammatory infiltration of cardiac tissue. Its preparation, Compound Danshen Dripping Pills, has been evaluated in clinical trials as a cardioprotective supplement to anthracycline-based chemotherapy. In treated patients, the results were preserved LVEF and reduced cardiac biomarker elevation (Zhang et al., 2012).

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4.11 Grape Seed Extract (Proanthocyanidins)

Oligomeric proanthocyanidins are the most potent antioxidants. It is obtained from Vitis vinifera grape seed extract. Its free radical elimination capacity is about 20-fold greater than that of vitamin C and 50-fold greater than that of vitamin E, as evidenced by in vitro studies. Against doxorubicin, it has demonstrated significant cardioprotective activity. For paclitaxel-induced toxicity, it showed neuroprotective activity. Its clinical investigations are limited but ongoing. Its potency as an antioxidant and safety profile make it a high-priority candidate.

4.12 Licorice Root (Glycyrrhiza glabra)

Its main constituent is glycyrrhizin, which has anti-inflammatory, hepatoprotective, and mucosal protective properties. Its efficacy for the prevention and treatment of chemotherapy-induced oral mucositis is evidenced. A trial indicated that liquorice root mouthwash reduced the severity and duration of 5-fluorouracil-induced oral mucositis. With its mucoprotective mechanism, it involves the stimulation of mucin secretion, suppression of mucosal inflammatory cytokines, and promotion of epithelial cell proliferation (Raeessi et al., 2012).

CHAPTER 5

SUMMARY OF KEY RANDOMISED CONTROLLED TRIALS OF HERBAL AGENTS AS Supplements Compared to Chemotherapy

Herbal Agent	Author (Year)	n	Design	Chemo therapy	Inter vention	Primary Outcome	Key Finding	Onco logical Safety
Ginger	Ryan et al. (2012)	576	RCT, DB, PC	Multiple (various)	0.5 g or 1.0 g/day × 6 days	Acute nausea severity	Significant reduction in acute CINV	Not assessed
Silymarin	Ladas et al. (2010)	50	RCT, DB, PC	6-MP + MTX (ALL)	5.1 mg/kg/day × 28 days	Serum AST/ALT	Significant NT-AST reduction	No difference in relapse rates
Ginseng	Barton et al. (2013)	364	RCT, DB, PC	Multiple (various)	2,000 mg/day × 8 weeks	MFSI-SF fatigue score	Significant fatigue reduction	Not assessed
Nano-curcumin	Panahi et al. (2014)	160	RCT, DB, PC	Multiple (various)	80 mg/day × 8 weeks	Nausea, vomiting, fatigue	Significant symptom reduction	Not assessed

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Curcumin	Saadati et al. (2019)	70	RCT, DB, PC	Docetaxel (breast)	500 mg/day × 3 cycles	Hepatotoxicity, neuropathy	Significant attenuation of both	No difference in response
Astragalus	McCulloch et al. (2006)	2.815	Meta-Hepatotoxicity (Ts)	Platinum based (NSCLC)	Various AMS formulations	1-year survival, response	Significant survival and immune benefit	Improved tumor response
Ashwagandha	Biswal et al. (2013)	100	RCT, DB, PC	Multiple (various)	2,000 mg/day × 6 months	Quality of life, fatigue	Significant QoL improved	Not assessed
Nigella sativa	Bamosa et al. (2010)	40	RCT, DB, PC	Cisplatin based	2 g/day	Nephrotoxicity biomarkers	Trend toward renal protection	Not assessed

DB = double blind; PC = placebo controlled; CINV = chemotherapy induced nausea and vomiting; MTX = methotrexate; 6-MP = 6 mercaptopurine; ALL = acute lymphoblastic leukaemia; MFSI-SF = Multidimensional Fatigue Symptom Inventory; AMS = Astragalus membranaceus based supplement; NSCLC = non small cell lung cancer; QoL = quality of life.

STRENGTH OF EVIDENCE AND STUDY LIMITATIONS

The clinical evidence for herbal medicine in conjunction with chemotherapy supportive care requires acknowledgement of data and statistics. The trials and publications done so far are not enough. We need to make it into definitive research, trials, and clinical settings. The strength of evidence is assessed using the framework, GRADE (Grading of Recommendations Assessment, Development and Evaluation). It indicates the range of the herbal agents reviewed today, from low to moderate. Ginger for acute CINV and ginseng for cancer-related fatigue have the most clinical evidence. It is supported by large-scale multicentre RCTs, utilising standardised interventions, outcome measures and adequate procedures. It is graded as moderate quality evidence.

Silymarin for chemotherapy-induced hepatotoxicity is supported by a smaller number of RCTs. It has a low-to-moderate evidence grade. Other herbal agents such as curcumin, ashwagandha, thymoquinone, and Boswellia stand at a low level of quality, with small sample sizes, single-centre designs, limited follow-ups and inadequate procedures in available trials. For their adequate results, further clinical investigations need to be done.

There are several methodological limitations across the herbal oncology trial literature.

1. First and foremost, there is the absence of standardisation in herbal preparations. The significant variations are seen in botanical species, plant part used, extraction method, phytochemical concentration, and form of administration.
2. Second, the published trials are insufficient to determine the moderate effect and have adequate power. Such as quality of life, toxicity outcomes lead to a risk of inaccurate findings and affect the size of positive trials.
3. Third, the assessment of oncology is also a question mark. Either the herbal supplements

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interfere with the chemotherapy's anti-tumour efficacy. It is not investigated in the clinical trial literature.

The oncological safety gap is a barrier in the clinical implementation of herbal supplements. It is urgently required to increase the evidence base for protocols, standardisation of herbal preparations, phytochemical characterisation, and adequate data for toxicity and oncological efficacy.

CHAPTER 7
PRINCIPAL CYP450-MEDIATED HERB-DRUG INTERACTIONS OF CLINICAL RELEVANCE IN ONCOLOGY

Herbal Agent	CYP Enzyme(s) Affected	Direction	Chemotherapy Drugs at Risk	Clinical Consequence	Evidence Level
St John's Wort	CYP3A4, Pgp	Induction	Irinotecan, imatinib, taxanes, and vinca alkaloids	Reduced drug exposure; compromised efficacy	Well established (clinical)
Grapefruit /furanocoumarins	CYP3A4	Inhibition	Erlotinib, lapatinib, oral taxanes, sunitinib	Increased drug exposure; amplified toxicity	Well-established (clinical)
Curcumin (high-dose)	CYP3A4, CYP2C9, Pgp	Inhibition	Docetaxel, paclitaxel, and imatinib	Potential increased exposure; theoretical toxicity risk	Preclinical/ limited clinical
Quercetin	CYP3A4, CYP2C8, Pgp	Inhibition	Paclitaxel, docetaxel	Increased oral bioavailability; toxicity risk	Preclinical
EGCG	CYP3A4, OATP1B1	Inhibition	Methotrexate, targeted agents	Altered drug disposition	Preclinical
Piperine	CYP3A4, CYP1A2, Pgp	Inhibition	Multiple CYP-substrate agents	Altered pharmacokinetics	Preclinical/ limited clinical

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Garlic extract	CYP2E1, CYP3A4	Inhibition / induction	Saquinavir, warfarin	Altered metabolism	Limited clinical
Echinacea	CYP3A4, CYP1A2	Mixed	Multiple	Unpredictable interaction risk	Preclinical

Pgp = P-glycoprotein efflux transporter; OATP1B1 = organic anion transporting polypeptide 1B1.

DISCUSSION

8.1 Interpretation of Key Findings

The key findings in this review are that when the selected herbal phytochemicals are used as a supplement to chemotherapy within the integrative oncological framework, it demonstrates meaningful and coherent improvements in the reduction of chemotherapy-induced adverse effects. The combination of preclinical data, pharmacological validity, and ever-growing clinical trial evidence provides a foundation for **synergistic oncology**. The important limitations regarding the safety, standardisation, and oncological efficacy are discussed throughout this review. The integrated interpretation of direct clinical and scientific significance is discussed above.

1. The first and foremost is the relationship between the herbal phytochemical cytoprotection and conventional chemotherapy cytotoxicity. This relationship can be assessed from differential oxidation biology, gene expression profiles, and transfer of signals between malignant and non-malignant cells. The Nrf2-ARE cytoprotective pathway is targeted by curcumin, EGCG, sulforaphane, and multiple other phytochemicals. This pathway is suppressed in various tumour cell types through epigenetically mediated silencing of Nrf2 or activation of its negative regulators. Therefore, it makes the tumour cells incapable of effective antioxidant responses to chemotherapy-induced oxidative stress. Simultaneously, it allows activation of phytochemical-mediated Nrf2 to protect normal tissues. This mechanism indicates the distinctive pharmacological characteristic of natural synergistic oncology.
2. The second theme is the multidimensional effects of herbal phytochemicals. Conventional antiemetics, haematopoietic growth factors, and nephroprotective agents particularly focus on a single toxicity domain through receptor-level mechanisms. It is effective for a specific target and provides no benefit for multiple toxicity profiles. On the other side, curcumin shows antioxidant, anti-inflammatory, hepatoprotective, nephroprotective, neuroprotective, and immunomodulatory properties. It offers a theoretical and preclinical advantage in therapeutic interventions. This multidimensionality is beneficial for cancer patients having multisystem toxicities, e.g., nephrotoxicity, peripheral neuropathy, and nausea.
3. The third one is the concern about the clinical significance of treatment compliance, from toxicity reduction to oncological benefits. The central argument is that it not only improves the patient's comfort and quality of life but also reduces the severity of toxicities.

8.2 Gaps in Current Literature

The identification of gaps in the research, trial and publication is mandatory to design a future search agenda. Several gaps of scientific and clinical importance can be identified from this review.

1. The most consequential and the one with the greatest implications is the absence of clinical data. The data address the question of whether herbal supplements interfere with the chemotherapy's anti-tumour efficacy. Addressing this gap required a large-scale trial and research

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work. This demands a greater investment in research infrastructure and funding.

2. The second critical gap is the interaction of herbal supplements and chemotherapy drugs. Despite preclinical evidence of CYP450-mediated interaction for herbal supplements, the evaluation of the effect of standardised herbal supplements is absent from the published literature. The management of this interaction relies on the in vitro enzyme inhibition data and animal pharmacokinetic studies.

3. The third gap is to investigate the role of herbal medicine in cancer patients. It is neglected in the existing trial literature. The evidence for the herb-drug interaction and cytoprotection is insufficient. It represents an urgent need to prioritise research in this domain.

The long-term safety and tolerance of the use of herbal supplements throughout chemotherapy courses have been evaluated in very few trials. Most published studies are limited to the supplementation period of four to twelve weeks, which does not indicate the duration of regular clinical use. It requires evaluation in well-designed studies.

8.3 Integrative Oncology: Future Direction

The advancement of integrative oncology as a discipline is defined as the combination of three rapidly evolving patterns. It includes;

➔ Patients demand personalised, quality-of-life cancer care,

➔ Supporting specific interventions for clinical use,

➔ Validation of integrative oncology institutes within cancer centres and professional guidelines

The future clinical application of herbal medicine within this evolving integrative oncology requires several interconnected domains. These domains are scientific, regulatory, educational, and institutional development.

From a scientific point of view, for safe and effective herbal supportive care, it is mandatory to use selected herbal interventions with a dose based on patient profile, tumour characteristics, and monitoring. For the personalised management of herb-drug interactions in clinical practice, the patient's plasma metabolite profile must be used. In this profile, monitor the individual's metabolic phenotypes and the pharmacokinetic consequences of herbal supplementation.

At the institutional level, for improving the safety and quality of herbal supplementation, it is mandatory to establish integrative oncology services within cancer centres. It will provide systematic assessment, clinical guidance, and monitoring of the use of complementary medicine in all oncology patients.

RECOMMENDATIONS FOR FUTURE RESEARCH

To advance the use of herbal medicine in oncological supportive cases requires clinical guidance and safe implementation. Based on the analysis presented throughout this review, the future recommendations are proposed below:

9.1 Recommendation 1: Conduct thoroughly supervised RCTs with oncological efficacy as primary and secondary outcomes

The most urgent research priority is to design and conduct controlled trials. Evaluate both the efficacy of herbal supplementations and their impact on tumour response rates and overall survival. No herbal agent should be added to recommendations until credible evidence has been found. It does not compromise chemoantitumour efficacy. Trials must be multicentric; they will be adequately designed and powered, with a minimal sample size. It should be conducted in collaboration between integrative oncology and conventional oncology. In this way, it will ensure the credibility required for its application in oncology practices.

9.2 Recommendation 2: Mandatory phytochemical standardisation and comprehensive analysis in all clinical trials

The clinical trials should be required as a prerequisite for ethical approval and journal publications. It will provide complete phytochemical properties, including botanical Latin binomial nomenclature, used part,

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extraction method and ratio, and absence of adulterants, heavy metals and contaminants. The plasma pharmacokinetic profiling of the active constituent should be included in trials as a verification measure. It will allow the correlation of plasma concentrations with clinical outcomes. It also facilitates dose optimisation with different pharmacokinetic profiles.

9.3 Recommendation 3: Prioritise potential clinical pharmacokinetic interaction studies

These studies employing herbal preparation at standard doses in cancer patients should be conducted for the most widely used herbal supplements. It includes curcumin, EGCG, quercetin, and Astragalus polysaccharides. These studies will validate the plasma concentration for both herbal constituents and the chemotherapeutic drugs.

9.4 Recommendation 4: Develop and validate high-bioavailability herbal formulations for clinical research

For those phytochemicals with preclinical evidence but limited in clinical terms, such as curcumin, a trial must be conducted to check their efficacy. The development of pharmaceutical-grade, high-bioavailability delivery systems and their systematic clinical pharmacokinetic characterisation must be prioritised. Clinical trials of formulations should be monitored to confirm the relevant systemic exposure in enrolled patients. It will enable meaningful interpretation of clinical efficacy and safety.

9.5 Recommendation 5: Establish international multicentre herbal oncology research consortia

Without the establishment of an international multicentre research with cooperative clinical trials of conventional oncology, the limitations which characterise the current herbal oncology evidence base cannot be resolved. The small single-trial centre, inadequate statistical power, publication bias in research institutes and absence of standard outcomes cannot be systemically resolved. An international herbal oncology clinical trial together with integrative medicine, pharmacology, oncology and regulatory science expertise should be established. This will design, conduct and publish multicentre randomised trials of standard herbal supplements by using protocols, quality control, and an analysis plan. It will also address the range of methodological deficiencies that limit the clinical efficacy of herbal oncology.

CONCLUSION

The evidence analysed and put together in this paper establishes synergistic oncology. The integration of herbal phytochemicals into conventional chemotherapy care as a scientific way of clinically framework. To get its clinical potential requires rigorous research, regulatory reform and clinical development. Herbal medicine has been used as a supplement by large numbers of cancer patients without clinical guidance.

The ethical and scientific necessity is clear; thorough, meticulous, and interdisciplinary research and clinical application must be implemented to get evidence for herbal supportive care. It is not to validate the lack of critical acceptance but to determine the quality of evidence that will allow clinicians to guide patients properly. This guidance will be away from the unacceptable risks and toward a model of integrative cancer care in which herbal and conventional medicine work together in the patient's best interest.

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