



## ANCIENT INDIAN AND CONTEMPORARY DIETARY FACTORS TO PLAUSIBLY REDUCE CHEMOTHERAPY INDUCED LEUKOPENIA (CIL): A COMPREHENSIVE & NARRATIVE REVIEW

Priya Darshane and Avdhoot Pandit

Department of Ayurveda & Yoga, Tilak Maharashtra Vidyapeeth, Mukund Nagar, Pune-411037, Maharashtra

### ARTICLE INFO

#### Article History:

Received 06<sup>th</sup> April, 2023

Received in revised form 14<sup>th</sup>

May, 2023

Accepted 23<sup>rd</sup> June, 2023

Published online 28<sup>th</sup> July, 2023

#### Key words:

Chemotherapy, Leukemia, *Ayurved*,  
Immunity, Diet

### ABSTRACT

**Objective:** Leukopenia is the most commonly experienced side effect of cancer treatments especially chemotherapy. This systematic review assesses whether there are any dietary factors which can have plausible effect on reducing the CIL (Chemotherapy Induced Leukopenia).

**Methods:** The search for immune enhancing dietary factors was carried out using the following databases; Google Scholar, Excerpta Medica Database (EMBASE), Public/Publisher MEDLINE (PubMed), Research gate and ELSEVIER. Also the ancient Indian literature particularly *Ayurvedic* scriptures such as *Chikitsa Prabhakar*, *Ayurved for Cancer*, *CharakSamhita*, *Sushrut Samhita*, *Bhavaprakshetc* and modern nutritional sciences' books were also studied comprehensively for the collection of references to augment immunity via diet. The related researches were meticulously studied with the aim to discover the dietary factors which will supplement immunity to reduce or lessen the risk of Chemotherapy Induced Leukemia (CIL).

**Results:** The review evidently explains the benefits of certain research assessed indigenous food components such as ginger, *Yashti-madhu* (licorice), betel leaf, *Triphala*, *Neem*, *Amla*, *Giloy*, *Punarnava* and also certain phytochemicals like alkaloids, polysaccharides, phenolic compounds, glycosides, anthocyanins, saponins, sterols etc. towards credibly increasing WBC count by immunomodulation and immuno-stimulation.

**Conclusion:** Dietary phytochemicals from certain indigenous herbs and foods have prominently exhibited anti-metastatic properties as well as immune-modulating activities. Hence these dietary phytochemicals from indigenous herbs and foods have been studied in depth to aid in reducing the risk of above mentioned side effect. Most of them can be safely used in the prevention of CIL once chemotherapy is commenced.

Copyright © The author(s) 2023. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

### INTRODUCTION

Chemotherapy is the main significant constituent of cancer treatment and most of the patients undergo chemotherapy at some or the other point of time during their course of treatment. However, chemotherapy drugs are well known to cause various side effects and adverse events such as chronic fatigue, anorexia, bone ache, nausea, vomiting and diarrhea, burning micturition, alopecia, cognitive disturbances and myelosuppression.

Leukopenia is the most common side effect of chemotherapy. And it is clinically proven that chemotherapy induced leukopenia (CIL) delays chemotherapy treatment and reduces drug dose intensity which may compromise clinical outcomes in potentially curable cancers (5).

And hence the main motive behind writing this all inclusive review is to collect and present all the references regarding dietary factors which stimulate WBC production and enhance immunity to avoid opportunistic infections in cancer patients taking chemotherapy. Traditional Indian medicinal system; *Ayurveda* also owns many remedies to help immune-compromised patients. Thus the ancient Indian *Vedic*

(*Ayurvedic*) scriptures were also studied thoroughly for the above mentioned facts.

As the individuals surviving cancer already undergo immense medical treatments and are generally maintained on oral drugs to avoid the relapse of cancer; the efforts are taken to possibly reduce the medicinal load by trying to increase immunity via diet.

#### Chemotherapy Induced Leukemia (CIL)

Most of the cancer patients are treated with chemotherapy as a predominant treatment of controlling cancer. Chemotherapy induced leukemia (CIL) is a common and adverse event of chemotherapy experienced by almost all the cancer patients. Leukopenia is the most common side effect of chemotherapy which usually decreases immune function and further leads to serious fatal infections (18). Over 5% of cancer patients develop chemotherapy-induced sepsis that is associated with 8.5% of all cancer deaths (23).

Many patients are treated with moderate to high toxicity chemotherapy drugs, including doxorubicin/epirubicin, paclitaxel/ docetaxel, and cyclophosphamide with or without 5-fluorouracil. Although it is an effective way to manage

\*Corresponding author: Priya Darshane

Department of Ayurveda & Yoga, Tilak Maharashtra Vidyapeeth, Mukund Nagar, Pune-411037, Maharashtra

cancer cells, it is also harmful to the hematopoietic system. Previous clinical trials demonstrated that taxane and cyclophosphamide can cause bone marrow suppression (leukopenia, thrombocytopenia and anemia) (14, 6) and severe immunosuppression, which may lead to serious and fatal infections, including respiratory infections and sepsis (3).

Once leukopenia occurs, treatment schedules need be interrupted and the treatment course may even be discontinued. In the hospitals to-date, granulocyte colony-stimulating factor (G-CSF) is commonly administered to reduce the risks of leukopenic complications associated with chemotherapy (16). However, it can result in many problems, such as aching in the bones and muscles, dyspnea, chest pain, nausea, hypoxemia, anaphylaxis, syncope, and flushing (1, 9). And also, the G-CSF injection is conditional only for patients with a white blood cell (WBC) count of  $<1000/\mu\text{L}$  or an absolute neutrophil count (ANC) of  $<500/\mu\text{L}$  (8). Therefore, using a subcutaneous injection of G-CSF to prevent or treat CIL cannot benefit all oncologic patients (18).

Drug-free period is always clinically necessary in cancer patients receiving chemotherapy, so as to allow their immune systems to restore function. During this period nutrients can possibly have impact on raising their immunity by immunomodulation.

And hence nutritional approach may be the means of helping to raise cancer therapy to a new level of success as supplementing or supporting the body with natural phytochemicals cannot only reduce adverse side effects but improve also the effectiveness of chemotherapeutics. Various plant-derived compounds have shown to improve the efficiency of cytotoxic agents, decrease their resistance, lower and alleviate toxic side effects, reduce the risk of tumour lysis syndrome, and detoxify the body of chemotherapeutics. The personalised approach using various phytochemicals provides thus a new dimension to the standard cancer therapy for improving its outcome in a complex and complementary way (8).

### **Role of Phytochemicals in Reducing CIL**

A voluminous literature exhibits the positive effect of phytochemicals on sensitizing the hematopoiesis and ultimately strengthening the immune system. Many studies have now demonstrated that phytochemicals participate not only as antioxidants, but more specifically as selective modulators of signal transduction (2). Here the role of phytonutrients in stimulating hematopoietic cell components is studied in detail.

Phytochemicals are naturally occurring compound with bioactive potentials, which have potential immunostimulating activity. In plants, phytochemicals act as a natural defense system for host plants and provide color, aroma and flavor. More than 4000 of these compounds have been discovered until date. Besides, protection of plants these phytochemicals also possess therapeutic potentials such as anti-oxidant, anti-diabetic, memory enhancing, cholesterol lowering effects, adaptogenic property, anticancer, and immunomodulatory activity (21). Natural compounds with potential immunostimulating activity can be classified as high- and low-molecular compounds. Terpenoids, phenolic compounds, and alkaloids dominate among low-molecular immunomodulatory

compounds, polysaccharides dominate among the high-molecular weight compounds (22).

There are various novel synthetic immunostimulants exist in the medical market such as Levamisole, Thalidomide, Recombinant cytokines, Isoprinosines etc which have been proved to be useful in the treatment of certain cancers like melanoma, metastatic renal carcinoma, hairy cell leukemia, follicular lymphoma, metastatic melanoma, colon cancer, carcinoma of urinary bladder, AIDs related Kaposi's sarcoma etc (21). But their administration has own limitations such as certain adverse effects like CNS depression, hypotension, myocardial infarction, GI distress, teratogenicity, hypersensitivity, allergic manifestations etc.

As against this, natural phytochemicals such as alkaloids, polysaccharides, lectins, glycosides, phenolic compounds, flavonoids, tannins, anthocyanins, saponins, terpenoids and sterols have exhibited positive role as immunomodulants especially immunostimulants.

**Alkaloids:** They are the most efficient and therapeutically significant plant component. They are the most promising anticancer agents. Examples include nicotine, cocaine, morphine and codeine, quinine, reserpine, and they have a large demand worldwide. They exhibit marked physiological activity when administered to animals (15). Alkaloids possess anti-tumor activity (vinblastine and vincristine), antimicrobial (cepharanthine), analgesic activity (morphine) and are also known to enhance immune response and a large number of alkaloids are being investigated for their immunostimulating properties (21, 7). (Table 1)

**Polysaccharides:** Botanical polysaccharides exhibit a number of beneficial therapeutic properties, and it is thought that the mechanisms involved in these effects are due to the modulation of innate immunity more specifically macrophage function (17). Recent pharmacological studies demonstrated the polysaccharides fraction of *Angelica sinensis* had radio-protective effects in irradiated mice through modulation of proliferative response of hemopoietic stem cells. Recently, certain polysaccharides of microbial origin have been described that act as potent immunomodulators with specific activity for both T cells and antigen-presenting cells such as monocytes and macrophages (13). In one research study protein bound polysaccharides PSK and PSP have been isolated from distinct strains of mushrooms. PSK and PSP are classified as biological response modifiers that stimulate T-cell activation and induce IFN- $\gamma$  and IL-2 production. The biologic activity is characterized by their ability to increase white blood cell counts, IL-2 production and delayed-type hypersensitivity reactions. In addition, these polysaccharides have been shown to inhibit the growth of tumor cell lines and have in vivo antitumor activity. The antitumor activity has been evaluated in Japan for prevention of oesophageal, gastric, and lung cancer in humans with promising results (20). Certain more polysaccharides with immunomodulatory properties are listed in table 2. (Table 2)

$\beta$ -(1-3)-Glucans are derived from various strains of fungi and yeast. Glucans are generally glucose homopolymers. When treated with  $\beta$ -(1-3)-glucans, it led to the increase in proportion of neutrophils and eosinophils. They also alter the macrophage activity.  $\beta$ -(1-3)-Glucans shows both cellular and humoral immune response via increasing the activity of mononuclear cells and neutrophils and enhanced proliferation

of macrophages (4). Soluble  $\beta$ -(1-3)-glucans is known to prevent bacterial sepsis. Soluble  $\beta$ -(1-3)-glucans increases the number of circulating neutrophils and also bone marrow proliferation (25).

**Glycosides:** Pharmaceutically important glycosides include saponins and anthracin derivatives. Glycosides mainly participate in the stimulation of cardiac system, central nervous system stimulation and immune system, they also possess antimicrobial activity. (Table 3)

**Phenolic Compounds:** These are wide range plant substances possessing an aromatic ring bearing one or more hydroxyl substituent. The presence of phenols is considered to be potentially toxic to the growth and development of pathogens. This group includes flavonoids, tannins, and other phenols (21). (Table 4)

**Flavonoids:** Flavonoids are potent water-soluble super antioxidants and free radical scavengers which prevent oxidative cell damage have strong anti-cancer activity and protect against all stage of carcinogens (26). In terms of anti-cancer activity, they inhibit the initiation, promotion, and progression of tumors. In recent times, plant flavonoids have attracted attention of researchers as a potentially important dietary supplement for cancer patients as they act as chemo protective agents (27). (Table 5)

**Anthocyanins, Tannins, Saponins and Sterols:** Anthocyanin isolates and anthocyanin-rich mixtures of bioflavonoid may provide protection from DNA cleavage, estrogenic activity (altering development of hormone-dependent disease symptoms), enzyme inhibition, boosting production of cytokines (thus regulating immune responses) (29).

Many physiological activities such as stimulation of phagocytic cells, host-mediated tumor activity and a wide range of anti-infective action have been assigned to tannins. (15.)

Modern researchers found that saponins have antitumor effect on many cancer cells. Several saponins inhibit tumor cell growth by cell cycle arrest and apoptosis (31).

It has been postulated that the sterols in a specific ratio could reinstate a balance between the Th1-Th2 cells, a delicate balance that determines the final outcome of the immune response (32.).

All of the above discussed phytonutrients exhibit the potential to act as immunostimulants in some or the other way. Immunomodulation and immunity augmentation is further possible by applying some means mentioned in ancient Indian Medicinal Science; *Ayurveda*.

The role of plant extracts and Ayurvedic polyherbal preparations in treating various ailments has been acknowledged since time immemorial. Studies based on the effect of these extracts in treatment of different diseases have also been well documented. Indian medicinal literature also emphasizes the synergistic effect of polyherbal drugs in restoring and rejuvenating immune system (35). Further these herbal formulations can be a better alternative for allopathic immunomodulators.

According to Ayurveda, certain herbal extracts and their formulations or combinations certainly help in leukocyte count strengthening. The facts mentioned in these ancient Ayurvedic scriptures are proved scientifically as well.

1. **Licorice:** Research has shown that licorice (*Jyeshthmadh/ Yashtimadhu*) is a potential specific immune stimulator. Licorice, the dry roots of *Glycyrrhiza glabra* L. (Fabaceae), is considered one of the oldest and most widely used herbal drugs around the world. Study has shown that licorice extract stimulates the activation of lymphocytes, mainly T cells (33).
2. **Triphala:** In one study, oral administration of *Triphala* (*Terminalia chebula*, *Terminalia bellerica* and *Emblca officinalis*) appeared to stimulate the neutrophil functions (34). Another study concludes that aqueous extracts of the individual constituents of *Triphala* reportedly enhance especially the macrophage activation due to their free radical scavenging activity and the ability to neutralize reactive oxygen species (35).
3. **Neem (*Azadirachtaindica*):** Many studies have exhibited the use of *Neem* extracts to augment immune function. One study exhibits significant result with respect to effect of *Neem* on leucocyte count. The study concluded that efficacy of *Neem* leaf preparation is comparable to granulocyte colony stimulating factor (GCSF) in its ability to protect against leukocyte apoptosis induced by cisplatin and 5-fluorouracil therapy. It emphasizes on use of *Neem* leaf preparation as a better choice of treatment in chemotherapy for cancer because GCSF is tumor promoting, angiogenic and expensive (36, 50, 51). In one more study *A. indica* treatment caused a significant increase in WBC counts as was seen in mice that received only aqueous *Neem* leaf extract treatment when compared to the control animals. Earlier, *A. indica* has been reported to enhance the WBC counts and was correlated with the growth restriction of murine carcinoma (37).
4. **Amla/ Indian gooseberry (*Phyllanthus emblica*):** *Phyllanthus emblica* has been extensively documented for possessing significant immunomodulating properties (51). *Amla* increases white blood cell counts and other measures of strengthened immunity in rodents given with *Amla* tonic. *Amla* inhibits the growth and spread of various cancers like breast, uterus, pancreas, stomach and liver cancers. It can prevent and/or reduce the side effects of chemotherapy and radiotherapy. More than 18 compounds were identified in *amla* fruit which can exert anti-proliferative activity on gastric and uterine cancer cells (39). The main mechanism behind its activity is by enhancing Natural Killer (NK) cell activity in various tumor cells. Emblicanin A & B of *amla* fruit are reported to possess strong antioxidant and anti-cancer properties (38).
5. **Guduchi/ Giloy (*Tinospora cordifolia*):** *Guduchi/ Giloy* is a climbing shrub widely used in the ethno-medicinal systems across the globe since ancient times (48, 49). The whole plant is used for therapeutic purpose. It is bitter but non-toxic and possesses potential ability to scavenge free radicals. Its immunomodulatory properties are well documented. In one study, **T. cordifolia** stem and leaf extracts significantly increased WBC levels in mice (40). Another study concluded that *Tinospora cordifolia* significantly improved immunity in children and proposed that it can be used as an adjuvant to

vaccination (41). One study described that *Tinospora cordifolia* led to activation of macrophages and as macrophages are the first line of defence in our body and play a crucial role in innate (nonspecific) and adaptive (specific) immunity, it is an important finding to support the immunostimulant action of the drug (42). Furthermore another study on male Wistar rats using alcoholic extract of *Tinospora cordifolia* also reported an increase in the white blood cell (WBC) counts, bone marrow cellularity, serum Ig concentrations, further substantiating the immunomodulatory potential of this plant (43). One more research proved that administration of *Tinospora cordifolia* stem extract to mice (200 mg/kg, i.p, daily for 5 days) increased the total white blood cell count significantly. It also increased bone marrow cellularity and  $\alpha$ -esterase positive cells in bone marrow indicating increased maturation of stem cells. Administration of the extract was also found to significantly increase humoral immune response. **Tinospora** extract reduced solid tumour growth and synergistically acted with cyclophosphamide in reducing (83%) the animal tumours (44).

6. **Punarnava (*Boerhavia diffusa*):** *Boerhavia diffusa* has been widely studied for its chemical constituents and therapeutic activities (48, 49). Punarnavine is an alkaloid dominantly present in *Punarnava*. In one study, the effect of Punarnavine on the immune system was analysed. Intraperitoneal administration of Punarnavine (40 mg/kg body weight) was found to enhance the total WBC count on 6<sup>th</sup> day. Bone marrow cellularity and number of alpha-esterase positive cells were also increased by the administration of Punarnavine (45).
7. **Betel Leaf (*Piper betle*):** *Piper betle* leaves have been found to exhibit antioxidant and anticarcinogenic activities (46, 48, 49).
8. **Ginger (*Zingiber officinale Roscoe*):** Ginger has been widely used for various beneficiary effects on body (48, 49). Among many studies, one study significantly confirmed that fish fed with powdered ginger rhizome showed significant immune-stimulatory effect, increasing WBC, haematocrit (Hct), RBC values compared with the control group (p < 0.05) (47). Many researches confirm the similar results for ginger.
9. **Shigru (*Moringa oleifera*):** Moringa is a nutrient-dense herb that is considered a powerhouse of vitamins, minerals, and antioxidants. It is believed to have immune-stimulating properties and may support immune system function. Moringa leaf extracts have shown potential immunomodulatory effects, although more research is needed in this area (52).






### Summary and Future Prospective

As chemotherapy is an integral part of most cancer treatments, chemotherapy induced Leukopenia (CIL) is a common, life threatening side effect of the procedure. Dietary phytochemicals from certain indigenous herbs and foods have prominently exhibited anti-metastatic properties as well as immune-modulating activities. Hence these dietary phytochemicals from indigenous herbs and foods have been studied in depth to aid in reducing the risk of above mentioned

side effect. Most of them can be safely used in the prevention of CIL once chemotherapy is commenced.



Further pre-clinical and clinical studies can be more effective in confidently stating their use as a treatment to prevent CIL.



**Table 1** Alkaloids as Immunomodulators

Alkaloid	Source	Mechanism of Action
Piperine <i>Piper longum</i>	 (Long pepper/ Pippali)	Increases total WBC count, bone marrow cellularity, total antibody production (19)
Berberine <i>Hydrasti canadensis</i>	 (Golden seal)	Significant reduction of plasma TNF- $\alpha$ , IFN- $\gamma$ and NO levels(11)
Tetrandrine <i>Stephania tetrandra</i>	 (Han Fang Ji)	Suppress cytokine production Inhibits NF- $\kappa$ B mediated release of inflammatory factors (10, 24)
Sinomenine <i>Sinomenium acutum</i>	 (Orient vine stem)	Graft survival (12)
Girinimbine and carbazole <i>Murraya koenigii</i>	 (Curry leaves/ Kadipatta)	toxicity against HCT-166 colon cancer cells (7)




\*WBC: White blood cell, TNF- $\alpha$ : Tumor necrosis factor alpha, IFN- $\gamma$ : Interferon gamma, NO: Nitric oxide, NF- $\kappa$ B: Nuclear factor-kappaB, HCT 166: human colon cancer cell line

**Table 2** Polysaccharides as Immunomodulators

Polysaccharide	Source	Mechanism of Action
Angelica sinensis	 (dong quai)	Modulation of proliferative response of hemopoietic stem cells
Polysaccharide Krestin (PSK) and Polysaccharopeptide (PSP)	 ( <i>Polyporus versicolor</i> - 'cloud)	Inhibit the immunosuppressive cytokine transforming growth factor beta





Galactose, Mannose. from <i>Cyamopsis tetragonoloba</i> (seed)		Anti-tumor, Anti-oxidant
$\beta$ -(1-3)-Glucans (yeast)		Increase the number of circulating neutrophils and also bone marrow proliferation

**Table 3** Glycosides as Immunomodulators

Glycoside	Source	Mechanism of Action
Aucubin <i>Plantago major</i>	 (broad leaf plantain) (Mango)	Enhances lymphocyte proliferation and secretion of IFN- $\gamma$
Mangiferin <i>Mangifera indica</i>		Enhances the production of IgG1 and IgG2b
Eupalitin-3-O- $\beta$ -D-galactopyranoside <i>Boerhaaviadiffusa</i>	 (Punarnava)	Inhibited PHA-stimulated proliferation of peripheral blood mononuclear cells IL-2 and TNF- $\alpha$ .



\*PHA: Phytohaemagglutinin, IL: Interleukin, TNF- $\alpha$ : Tumor necrosis factor alpha, IFN- $\gamma$ : Interferon gamma, IgG: Immunoglobulin G



**Table 4** Phenolic Compounds as Immunomodulators

Phenolic Compounds	Source	Mechanism of Action
Gallic acid	 (amla, berries)	B-cell proliferation, inhibition of mast cell degranulation
Ellagic acid <i>Punica granatum</i>	 (Pomegranate)	Anti-proliferative and antioxidant
Chlorogenic acid <i>Plantago major</i> , Ferulic acid <i>Plantago major</i> ,	 (Broad leaf plantain)	Enhances lymphocyte proliferation and secretion of IFN
P-Coumaric acid <i>Plantago major</i> Curcumin <i>Curcuma longa</i>	 (Turmeric)	Enhances bone marrow cellularity, $\alpha$ esterase positive cells and phagocytic activity. Inhibits IL-2 expression and NF- $\kappa$ B

\*IFN: Interferon, IL: Interleukin, NF- $\kappa$ B: Nuclear factor-kappaB

**Table 5** Flavonoids as Immunomodulators

Flavonoid	Source	Mechanism of Action
Centaurein <i>Bidenspilosa</i>	 (Spanish needle)	Augmentation of IFN- $\gamma$ promoter activity
Apigenin 7-o- $\beta$ -D-Neohesperidoside, Vitexin and Orientin <i>Jatropha curcas</i>	 (Dravanti)	Stimulation of humoral and cell mediated immune response

Luteolin , Baicalein <i>Plantago major</i>	 <p>(Broad leaf plantain)</p>	Enhances lymphocyte proliferation and secretion of IFN
Quercetin-3-O-rutinosi de <i>Urticadioica</i>	 <p>(Stinging nettel)</p>	Immunomodulat ion

\*IFN- $\gamma$ : Interferon gamma

### Conflict of Interest

The authors declare that they have no conflict of interest.

### References

1. Aras, E., Bayraktar-Ekincioglu, A., & Kilickap, S. (2020). Risk assessment of febrile neutropenia and evaluation of G-CSF use in patients with cancer: A real-life study. *Supportive Care in Cancer*, 28(2), 691–699. <https://doi.org/10.1007/s00520-019-04879-x>
2. Bland, J. S. (2021). Application of phytochemicals in immune disorders: Their roles beyond antioxidants. *Integrative Medicine*, 20(5), 16–21.
3. Brand, J. S., Colzani, E., Johansson, A. L. V., Giesecke, J., Clements, M., Bergh, J., Hall, P., & Czene, K. (2016). Infection-related hospitalizations in breast cancer patients: Risk and impact on prognosis. *Journal of Infection*, 72(6), 650–658. <https://doi.org/10.1016/j.jinf.2016.04.003>
4. Wakshull, E., Brunke-Reese, D., Linderthuth, J., Fisette, L., Nathans, R. S., Crowley, J. J., Tufts, J. C., Zimmerman, J., Mackin, W., & Adams, D. S. (1999). PGG-glucan, a soluble  $\beta$ -(1,3)-glucan, enhances the oxidative burst response, microbicidal activity, and activates an NF- $\kappa$ B-like factor in human PMN: Evidence for a glycosphingolipid  $\beta$ -(1,3)-glucan receptor. *Immunopharmacology*, 41(2), 89–107. [https://doi.org/10.1016/s0162-3109\(98\)00059-9](https://doi.org/10.1016/s0162-3109(98)00059-9)
5. Franklin, J., & Diehl, V. (2002). Current clinical trials for the treatment of advanced-stage Hodgkin's disease: BEACOPP. *Annals of Oncology*, 13, Suppl. 1, 98–101. <https://doi.org/10.1093/annonc/13.s1.98>
6. Fu, H., Chen, B., Hong, S., & Guo, Y. (2015). Acupuncture therapy for the treatment of myelosuppression after chemotherapy: A literature review over the past 10 years. *Journal of Acupuncture and Meridian Studies*, 8(3), 122–126. <https://doi.org/10.1016/j.jams.2014.09.003>
7. Isah, T. (2016, July–December). Anticancer alkaloids from trees: Development into drugs. *Pharmacognosy Reviews*, 10(20), 90–99. <https://doi.org/10.4103/0973-7847.194047>, PubMed: 28082790, PubMed Central: PMC5214563.
8. Sak, K., (2012). Chemotherapy and dietary phytochemical agents. *Chemotherapy Research and Practice*, 2012, article ID 282570. <https://doi.org/10.1155/2012/282570>
9. Khoury, H., Adkins, D., Brown, R., Vij, R., Westervelt, P., Trinkaus, K., Goodnough, L. T., & DiPersio, J. F. (2000). Adverse side-effects associated with G-CSF in patients with chronic myeloid leukemia undergoing allogeneic peripheral blood stem cell transplantation. *Bone Marrow Transplantation*, 25(11), 1197–1201. <https://doi.org/10.1038/sj.bmt.1702423>
10. Lai, J. H., Ho, L. J., Kwan, C. Y., Chang, D. M., & Lee, T. C. (1999). Plant alkaloid tetrandrine and its analog block CD28- costimulated activities of human peripheral blood T cells: Potential immunosuppressants in transplantation immunology. *Transplantation*, 68(9), 1383–1392. <https://doi.org/10.1097/00007890-199911150-00027>
11. Li, F., Wang, H. D., Lu, D. X., Wang, Y. P., Qi, R. B., Fu, Y. M., & Li, C. J. (2006). Neutral sulfateberberine modulates cytokine secretion and increases survival in endotoxemic mice. *Acta Pharmacologica Sinica*, 27(9), 1199–1205. <https://doi.org/10.1111/j.1745-7254.2006.00368.x>
12. Mark, W., Schneeberger, S., Seiler, R., Stroka, D. M., Amberger, A., Offner, F., Candinas, D., & Margreiter, R. (2003). Sinomenine blocks tissue remodeling in a rat model of chronic cardiac allograft rejection. *Transplantation*, 75(7), 940–945. <https://doi.org/10.1097/01.TP.0000056610.22062.03>
13. Mei, Q. B., Tao, J. Y., Zhang, H. D., Duan, Z. X., & Chen, Y. Z. (1988). Effects of Angelica sinensis polysaccharides on hemopoietic stem cells in irradiated mice. *Acta Pharmacologica Sinica*, 9(3), 279–282.
14. Moo, T. A., Sanford, R., Dang, C., & Morrow, M. (2018). Overview of breast cancer therapy. *PET Clinics*, 13(3), 339–354. <https://doi.org/10.1016/j.cpet.2018.02.006>
15. Okwu, D. E., & Okwu, M. E. (2004). Chemical Composition of *Spondias mombim* Linn Plants. *Journal of Environment & Sustainable Agriculture*, 6, 140–147.
16. Papakonstantinou, A., Hedayati, E., Hellström, M., Johansson, H., Gnant, M., Steger, G., Greil, R., Untch, M., Moebus, V., Loibl, S., Foukakis, T., Bergh, J., & Matikas, A. (2020). Neutropenic complications in the PANTHER phase III study of adjuvant tailored dose-dense chemotherapy in early breast cancer. *Acta Oncologica (Stockholm)*, 59(1), 75–81. <https://doi.org/10.1080/0284186X.2019.1670353>
17. Schepetkin, I. A., & Quinn, M. T. (2006). Botanical polysaccharides: Macrophage immunomodulation and therapeutic potential. *International Immunopharmacology*, 6(3), 317–333. <https://doi.org/10.1016/j.intimp.2005.10.005>
18. Shih, Y. W., Su, J. Y., Kung, Y. S., Lin, Y. H., To Anh, D. T., Ridwan, E. S., & Tsai, H. T. (2021). Effectiveness of acupuncture in relieving chemotherapy-induced leukopenia in patients with breast cancer: A systematic review with a meta-analysis and trial sequential analysis. *Integrative Cancer Therapies*, 20, 15347354211063884. <https://doi.org/10.1177/15347354211063884>
19. Sunila, E. S., & Kuttan, G. (2004). Immunomodulatory and antitumor activity of Piper longum Linn. and piperine. *Journal of Ethnopharmacology*, 90(2–3), 339–346. <https://doi.org/10.1016/j.jep.2003.10.016>

20. Ng, T. B. (1998). A review of research on the protein-bound polysaccharide (polysaccharopeptide, PSP) from the mushroom *Coriolus versicolor* (Basidiomycetes: Polyporaceae). *General Pharmacology: The Vascular System*, 30(1), 1–4. [https://doi.org/10.1016/S0306-3623\(97\)00076-1](https://doi.org/10.1016/S0306-3623(97)00076-1)
21. Venkatalakshmi, Vadhivel versus Brindha, P. Phytochemicals as immunomodulators. *International Journal of Green Pharmacy*, January–March, 2016, 10 (1); 2.
22. Wagner, H. (1999). Structural analysis of a rhamnoarabinogalactan and arabinogalactans with immunostimulating activity from *Calendula officinalis*. *Phytochem.*, 28, 2379–2383.
23. Williams, M. D., Braun, L. A., Cooper, L. M., Johnston, J., Weiss, R. V., Qualy, R. L., & Linde-Zwirble, W. (2004). Hospitalized cancer patients with severe sepsis: Analysis of incidence, mortality, and associated costs of care. *Critical Care*, 8(5), R291–R298. <https://doi.org/10.1186/cc2893>
24. Xue, Y., Wang, Y., Feng, D. C., Xiao, B. G., & Xu, L. Y. (2008). Tetrandrine suppresses lipopolysaccharide-induced microglial activation by inhibiting NF-kappaB pathway. *Acta Pharmacologica Sinica*, 29(2), 245–251. <https://doi.org/10.1111/j.1745-7254.2008.00734.x>
25. Goyal, S. R., Neha, A. Das J., Choden, S., & Kumar, P. (2021). Immunomodulatory potential of polysaccharides derived from plants and microbes: A narrative review. *Carbohydrate Polymer Technology and Applications*, 2, 1000044.
26. Urquiaga, I., & Leighton, F. (2000). Plant polyphenol antioxidants and oxidative stress. *Biological Research*, 33(2), 55–64. <https://doi.org/10.4067/s0716-97602000000200004>
27. Hertog, M. G. L., Hollman, P. C. H., & van de Putte, B. (1993). Content of potentially anticarcinogenic flavonoids of tea infusions, wines and fruit juices. *Journal of Agricultural and Food Chemistry*, 41(8), 1242–1246. <https://doi.org/10.1021/jf00032a015>
28. Elangovan, V., Sekar, N., & Govindasamy, S. (1994). Chemopreventive potential of dietary bioflavonoids against 20-methylcholanthrene-induced tumorigenesis. *Cancer Letters*, 87(1), 107–113. [https://doi.org/10.1016/0304-3835\(94\)90416-2](https://doi.org/10.1016/0304-3835(94)90416-2)
29. Rossi, A., Serraino, I., Dugo, P., Di Paola, R., Mondello, L., Genovese, T., Morabito, D., Dugo, G., Sautebin, L., Caputi, A. P., & Cuzzocrea, S. (2003). Protective effects of anthocyanins from blackberry in a rat model of acute lung inflammation. *Free Radical Research*, 37(8), 891–900. <https://doi.org/10.1080/1071576031000112690>
30. Okwu, D. E., & Okwu, M. E. (2004). Chemical Composition of *Spondias mombim* Linn Plants. *Journal of Environment & Sustainable Agriculture*, 6, 140–147.
31. Sulaiman, S. M., Rajashekha, G., Prakash, P. J., Singh, D. S., & Saleem, C. (2010). Immunoprophylactic activity of Immunol, a polyherbal formulation against dexamethasone induced immunosuppression in rats. *Journal of Pharmacology and Toxicology*, 5(6), 275–287. <https://doi.org/10.3923/jpt.2010.275.287>
32. Bouic, P. J., & Lamprecht, J. H. (1999). Plant sterols and sterolins: A review of their immune-modulating properties. *Alternative Medicine Review: A Journal of Clinical Therapeutic*, 4(3), 170–177.
33. Cheel, J., Onofre, G., Vokurkova, D., Tůmová, L., & Neugebauerová, J. (2010). Licorice infusion: Chemical profile and effects on the activation and the cell cycle progression of human lymphocytes. *Pharmacognosy Magazine*, 6(21), 26–33. <https://doi.org/10.4103/0973-1296.59963>
34. Srikumar, R., JeyaParthasarathy, N., & Sheela Devi, R. (2005). Immunomodulatory activity of triphala on neutrophil functions. *Biological and Pharmaceutical Bulletin*, 28(8), 1398–1403. <https://doi.org/10.1248/bpb.28.1398>
35. Belapurkar, P., Goyal, P., & Tiwari-Barua, P. (2014). Immunomodulatory effects of triphala and its individual constituents: A review. *Indian Journal of Pharmaceutical Sciences*, 76(6), 467–475.
36. Ghosh, D., Bose, A., Haque, E., & Baral, R. (2009). Neem (*Azadirachta indica*) leaf preparation prevents leukocyte apoptosis mediated by cisplatin plus 5-fluorouracil treatment in Swiss mice. *Chemotherapy*, 55(3), 137–144. <https://doi.org/10.1159/000211558>
37. Gangar, S. C., Sandhir, R., & Koul, A. (2010). Effects of *Azadirachta indica* on certain hematological parameters during benzo(a)pyrene induced murine forestomach tumorigenesis. *European Review for Medical and Pharmacological Sciences*, 14(12), 1055–1072.
38. Pandey, G. (2011). Some important anticancer herbs: A review. *International Research Journal of Pharmacy*, 2, 45–52.
39. Sharma, M., & Pandey, G. (2008). Studies on oestrogen induced uterine and ovarian carcinogenesis and effect of ProImmu in rats [PhD Thesis].
40. Sharma, V., & Pandey, D. (2010). Beneficial effects of *Tinosporacordifolia* on blood profiles in male mice exposed to lead. *Toxicology International*, 17(1), 8–11. <https://doi.org/10.4103/0971-6580.68341>
41. Sharma, D. N., & Sharma, A. (2015). *Tinosporacordifolia* Enhances Vyadhikshamatwa (immunity) in Children. *Journal of Phytopharmacology*, 4(4), 227–230. <https://doi.org/10.31254/phyto.2015.4408>
42. More, P., Pai, K., & Khind, G. (2011). Immunomodulatory effects of *Tinosporacordifolia* (Guduchi) on macrophage activation. *Biology and Medicine*, 3(2):134–40.
43. Aher VD, Wahi AK. Pharmacological Study of *Tinospora Cordifolia* as an Immunomodulator. *Int J Curr Pharm Res* 2010;2(4):52–4.
44. Mathew, S., & Kuttan, G. (1999). Immunomodulatory and antitumour activities of *Tinosporacordifolia*. *Fitoterapia*, 70(1), 35–43. [https://doi.org/10.1016/S0367-326X\(98\)00017-3](https://doi.org/10.1016/S0367-326X(98)00017-3)
45. Manu, K. A., & Kuttan, G. (2009). Immunomodulatory activities of Punarnavine, an alkaloid from *Boerhaaviadiffusa*. *Immunopharmacology and Immunotoxicology*, 31(3), 377–387. <https://doi.org/10.1080/08923970802702036>
46. Alam, B., Majumder, R., Akter, S., & Lee, S. H. (2015). Piper betle extracts exhibit antitumor activity by augmenting antioxidant potential. *Oncology Letters*, 9(2), 863–868. <https://doi.org/10.3892/ol.2014.2738>
47. Shokr. (2019). Professorelsayed. Effect of Ginger on Some Hematological Aspects and Immune System in Nile TILAPIA, 2019–2020.

48. Sharma, P. V. (Ed.). (2017). *CharakSamhita* (2nd ed., Vol. 1). Chaukhambaorientalia.
49. Sharma, P. V. (Ed.). (2012). *Susruta- Samhita* (1st ed., Vol. 3). ChaukhambaViswabharti.
50. *AstangaSamgraha of Vagbhata* (K. R. S. Murthy, Trans.; 9th ed., Vol. 1). (2018). Chaukhambha Orientalia.
51. Gangadharan, G. G. (Ed.). (2012). *Bhojankutuhalam* (R. Shankar, Trans.; 1st ed.). Indian Institute of Ayurveda & Integrative Medicine (IIAIM), FoundationFor Revitalization of Local Health Traditions (FRLHT).
52. Banks, J. E., Ackleh, A. S., Veprauskas, A., & Stark, J. D. (2019). The trouble with surrogates in environmental risk assessment: a daphniid case study. *Ecotoxicology (London, England)*, 28(1), 62–68. <https://doi.org/10.1007/s10646-018-1999-0>

\*\*\*\*\*