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Immunonutrition In Cancer Patients: Role Of Diet, Phytochemicals, And Traditional Indian Herbs In Modulating Treatment Outcomes

Satakshi Mishra[1], Charu Mehta[2], Mohit Kumar[3], Rohit Kumar[4], Dr. Ramesh Chandra[4]*

[1] Ph.D scholar, Faculty of ayurveda, Department of Shalya Tantra, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India. https://orcid.org/0009-0005-8108-9186 Gmail: shatakshi.ald12@gmail.com
[2] Ph.D scholar, Department of Swasthavritta and Yoga, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India. Email: charu.mehta2109@gmail.com, ORCID: 0009-0008-0626-218X
[3] Ph.D scholar, Department of Sangyaharan, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India. Email: mohitkumar.dsvv@gmail.com, ORCID: 0009-0003-2244-6986
[4] Ph.D scholar, Department of Kayachikitsa, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India. Email: rohit812797@gmail.com, ORCID: 0000-0001-7461-2956
[4] Ph.D scholar, Department of Sangyaharan, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India. Email: chandra0078530@gmail.com
** Corresponding Author: Dr. Ramesh Chandra, PhD Scholar, Department of Sangyaharan, Faculty of Ayurveda, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India. Email: chandra0078530@gmail.com*

Abstract

Cancer and its treatment are commonly linked to immune dysfunction, malnutrition and increased vulnerability to infection, which can negatively affect treatment tolerance and clinical outcome. There is increasing evidence that immunonutrition, meaning targeted nutritional strategies to modulate immune responses, plays a critical role in improving therapeutic efficacy and quality of life in cancer patients. Diet, bioactive phytochemicals and medicinal herbs have received greater attention for their immunomodulatory, anti-inflammatory and antioxidant properties, especially as adjuncts to conventional cancer therapies such as chemotherapy and radiotherapy. This review critically examines the role of immunonutrition in the context of cancer patients with a special emphasis on the impact of dietary constituents, plant-based phytochemicals and traditional Indian medicinal herbs in modulating immune function and treatment outcomes.

A systematic narrative review was conducted using electronic databases such as PubMed, Scopus, Web of Science, and Google Scholar, encompassing pertinent experimental, clinical, and review articles published between 2000 and 2025. We discuss important immunonutrients like arginine, glutamine, omega-3 fatty acids, vitamins and trace elements and major phytochemicals like curcumin, resveratrol, epigallocatechin gallate and quercetin. Furthermore, the evidence for immunomodulatory potential of traditional Indian herbs like Tinospora cordifolia, Withania Somnifera, Curcuma longa and Ocimum sanctum is systematically summarized.

The results indicate that immunonutrition might improve immune competence, reduce treatment-related toxicities, improve inflammatory and haematological parameters and increase overall treatment tolerance in cancer patients. However, heterogeneity of study designs, lack of large scale randomized clinical trials and concerns regarding standardization and herb–drug interactions are still significant challenges. In conclusion, immunonutrition is a promising supportive modality in integrative oncology, with a need for further well-designed clinical studies to establish standardized protocols and evidence-based guidelines for its safe and effective use in cancer care.

Keywords: Cancer, Immunonutrition, Phytochemicals, Medicinal Plants, Chemotherapy, Radiotherapy, Immune Modulation.

Introduction

Globally, cancer continues to be a major public health burden, and it is still one of the leading causes of morbidity and mortality throughout the world. Cancer incidence and mortality are increasing steadily worldwide, with millions of new cases diagnosed every year. The burden is growing due to an aging population, urbanization, lifestyle changes, environmental exposures and dietary transitions. A significant proportion of cancer deaths occur in low- and middle-income countries, indicating a need for affordable and supportive interventions to enhance patient outcomes alongside standard therapies [1,2].

Cancer is associated with profound changes in host immune function in addition to uncontrolled cellular proliferation. Tumour cells have several mechanisms to evade immune surveillance, including suppression of cytotoxic T-lymphocyte activity, dysregulation of cytokine signalling, impairment of antigen presentation and functional exhaustion of natural killer cells. This tumor-induced immune dysfunction is correlated not only with disease progression but also with reduced responsiveness to anticancer therapies and a higher susceptibility to infections [3,4].

Standard cancer treatment methods like radiation or chemotherapy can cause damage to your immune system. Radiation and chemotherapy are aimed at attacking the cancer cells, but because they attack all fast-growing cells, they will harm your healthy cells as well, including your bone marrow and intestinal immune cells. After these treatments, people are usually left with anaemia, neutropenia, lymphopenia, mucositis, fatigue, and systemic inflammation; these problems can all lead to negative health impacts (such as decreased quality of life, increased difficulty tolerating treatment, and decreased overall survival) [5-7].

Recently, there has been an increase in interest in the use and application of immunonutrition in the treatment of cancer and its impact on patients receiving treatment for cancer. Immunonutrition provides specific nutrients and bioactive dietary constituents that are intentionally consumed to modulate immune function, pathways of inflammation, and the metabolism of a patient. The main immunonutrients include arginine, glutamine, omega-3 fatty acids, nucleotides, vitamins, trace minerals, and plant-derived phytochemicals, and their effect on immune cell activity/function, cytokine production, oxidative stress, and tissue healing has been extensively researched. There is an increasing body of evidence demonstrating that immunonutrition may reduce the incidence of toxic effects from conventional cancer treatments, increase the competence of the immune system, and improve the clinical outcomes of patients receiving traditional cancer treatments if used as an adjunct to the traditional therapy [8-10].

There continues to be a significant gap in research with regard to the systematic investigation of the traditional herbs of India within the context of immunonutrition and their clinical outcomes in cancer patients, despite the growing body of research related to immunonutrition. Traditionally, botanicals such as Tinospora cordifolia (Guduchi), Withania somnifera (Ashwagandha), Curcuma longa (turmeric), and Ocimum sanctum (Tulsi) have been used because of their immunomodulatory, adaptogenic, and anti-inflammatory properties. Although limited preclinical and clinical data exists to support that those botanicals could be used for enhancing immune function and assisting patients with treatments, the scientific basis of using these herbs in creating evidence-based immunonutritional therapies has not been sufficiently investigated [11-13] .

Therefore, the aim of this review is to critically examine the role of immunonutrition in cancer patients, with a specific focus on diet, bioactive phytochemicals, and traditional Indian medicinal herbs in modulating immune function and treatment outcomes. By synthesizing mechanistic, experimental, and clinical evidence, this review seeks to highlight therapeutic potential, identify limitations, and propose future research directions for the safe and effective incorporation of immunonutrition into integrative cancer care.

The objective of this review was to assess the function of immunonutrition in patients with cancer, with emphasis on the impact of diet, the effect of bioactive phytochemicals and traditional Indian medicinal herbs on immune response and cancer treatment outcomes. This review synthesises evidence from mechanistic studies, laboratory studies and clinical research to show the therapeutic potential of immunonutrition; identify new research directions and highlight any limitations; and describe ways to safely and effectively integrate immunonutrition into the holistic treatment of cancer.

4. Methodology

A systematic review of previous research was used to assess the role of immunonutrition in patients with cancer, with particular emphasis on how dietary components, phytochemicals and traditional Indian medicinal herbs modulate immune function and treatment outcome, using systematic and transparent practices to conduct literature searches of existing clinical studies, including journal articles, documents, and reports.

Data sources/ data collection

Data was retrieved using four online databases: PubMed/Medline, Scopus, Web Of Science and Google Scholar.

A combination of Medical Subject Headings (MeSH) and free text key words were employed in the search strategy to identify relevant literature on the role of immunonutrition in cancer patients including articles on “Cancer Patients, Immunonutrition, Immune Modulation, Nutrition and Immune Response, Phytochemicals, Medicinal Plants, Traditional Indian Medicinal Herbs, Tinospora cordifolia, Withania somnifera, Curcuma longa, Chemotherapy, Radiotherapy.”

The Review Covered Literature Published from January 2000 To December 2025 To Include Both Foundational Studies and Recent Developments In The Areas Of Immunonutrition And Clinical Oncology Via Integrative Approaches.

The Review Included a Wide Variety of Scientific Evidence, Including:

- RCTs (Randomized Controlled Trials)
- Observational And Cohort Studies
- Experimental In Vitro and In Vivo Studies
- Systematic Reviews and Meta-Analyses
- The Use of Evidence-Based Narrative Reviews

All Relevant Data Was Extracted Manually, Grouped into Thematic Domains (I.E. Immune Mechanisms, Nutritional Components, Phytochemicals, Medicinal Herbs, And Treatment-related Outcomes), And Synthesized Qualitatively to Identify Consistent Patterns, Therapeutic Benefits, Limitations, And Gaps in Current Knowledge.

Cancer, Immunity, and Treatment outcomes

The immune system's major job is to detect and destroy malignant (cancerous) cells through a process known as "immune surveillance." Under normal physiological conditions, it accomplishes this task using both the innate (non-specific) and adaptive (specific) immune system components. At some stage during their development, however, malignant cells acquire the ability to evade immune detection and subsequently establish and, ultimately, progress as a tumor. The dynamic relationship developing between the tumor and the host immune system is best described by the concept of "cancer immunoediting," which consists of three phases: elimination, equilibrium, and escape [14]. During elimination, immune effector cells seek out and destroy newly developed malignant (tumor) cells. During the equilibrium phase, tumor cell growth is blocked as a consequence of immune-mediated pressure, while at the same time, less immunogenic tumor cell variants are selected. Ultimately, tumor cells escape from being controlled by the immune system through genetic and/or epigenetic processes, resulting in an established and clinically detectable malignant (tumor) disease [14,15]. The processes outlined will ultimately determine disease aggressiveness, therapeutic responsiveness, and long-term disease outcomes. Tumors use many different methods to evade detection and destruction by the immune system, including down-regulating tumor antigen expression, disruption of antigen processing and presentation, secretion of immunosuppressive proteins, and recruitment of regulatory immune cells into the tumor microenvironment. These various mechanisms collectively contribute to inducing immune tolerance, fostering a chronic inflammatory response, and/or inhibiting the development of effective anti-cancer immune responses, all of which impact disease evolution and treatment response [16,17].

Cytokines and Immune Cells in Cancer

T Lymphocyte (T Cells) - T lymphocytes are essential for developing adaptive immunity against cancer. T cytotoxic 8+ (CD8+) lymphocytes destroy malignant cells by recognizing and killing them through

the release of perforin-granzyme complexes and through interactions between the cells (Fas–Fas ligand pathway). CD4+ (helper) T lymphocytes provide additional support to the CD8+ cytotoxic lymphocytes by producing cytokines that promote antigen presentation to other immune cells and increase their activation through an increase in the number of immune cells at tumor sites.

In cancer patients, T-cell activity becomes exhausted from prolonged periods of exposure to tumor-sourced antigens and tumor-derived negative regulatory signals that result in reduced cellular proliferation, reduced cytokine secretion, and decreased cytotoxicity. Exhausted T cells express high levels of negative regulatory molecules (PD-1 and CTLA-4), which inhibit the ability of T lymphocytes to generate effective and stronger antitumor immune responses, and correlate strongly with poor clinical responses in patients.

NK Cells - NK cells are very important to the innate immune system and protect against malignant transformation in humans. NK cells identify and eliminate malignant cells without needing to first recognize specific tumor antigens (i.e., they kill misleadingly by detecting down-regulated or absent MHC class I molecules). The mechanisms responsible for killing tumor cells are mainly through direct lysis and cytokines (i.e., IFN-γ) and that these NK-cell-derived cytokines also help promote secondary immune responses. A large body of clinical and experimental data demonstrates an inverse correlation between the numbers of NK cells and the likelihood of patients with cancer having poor outcomes (higher likelihood of disease progression).

Reduced activity of natural killer (NK) cells has been demonstrated to correlate with the progression of tumors, the spread of tumors to other body sites (metastasis), and lower survival rates in various types of cancer based on clinical as well as experimental studies [22].

Cytokines are critical to regulating the balance between the immune system and cancer (homeostasis). Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) enhance inflammation in association with cancer (tumor-associated), promote angiogenesis (the formation of new blood vessels to supply tumors), promote dysregulation of the immune system, and contribute to cancer cachexia (wasting syndrome in cancer patients). In contrast, antigenically active cytokines such as interferon-γ (IFN-γ) and interleukin-2 (IL-2) enhance the immune response, enhance the proliferation of cytotoxic lymphocytes, and stimulate the generation of an anti-tumor (antigenic) response. [23, 24]

The unbalanced production of pro-cancerous (pro-tumorigenic) and anti-cancerous (antitumor) cytokines within the tumor microenvironment has a profound impact on immune function and how well the body responds to cancer treatment, as well as how long a person with cancer will live after being diagnosed [25].

The effects of chemotherapy/radiotherapy on immunity are complicated and often bidirectional; in other words, the way these 2 modalities impact an individual's immunologic response may vary depending on the individual as well as the combination of therapies being delivered to them. For example, both chemotherapy and radiotherapy may induce an immune response by creating more immune cells (lymphocytes) through immunogenic cell death (the killing of cancerous (tumour) cells in response to being killed by these treatments), increasing the release of antigens from dying tumour cells into the bloodstream and subsequently priming the immune system to recognize and attack any remaining tumour cells.

All of the above-mentioned factors (e.g., myelosuppression, chemotherapy-related oxidative stress/medications causing systemic inflammation, nutritional deficiencies, lymphocytes being destroyed by radiation) ultimately lead to a compromised immune system, which is referred to as treatment-induced immune suppression. Treatment-induced immune suppression is a significant contributor, along with chemotherapy/radiation dose reductions or treatment interruptions due to adverse events related to chemotherapy/radiation, to patients experiencing infectious complications, decreased overall quality of life and ultimately poorer survival outcomes. Recently, preserving the individual's immune function is believed to be a major factor in determining the therapeutic success of any given treatment modality.

Role of Tumor Microenvironment (TME) in Regulating the Immune Response and Response to Therapy: The TME is composed of a variety of (1) malignant cells, (2) stroma containing fibroblasts, endothelial cells, (3) immune effector cells, (4) components of extracellular matrix (ECM), and (5) soluble mediators. The TME is continuously remodeled by the TME in order to create an

immunosuppressive environment that allows for immune evasion and progression of disease [32]. The most important immunosuppressive populations located within the TME are (1) regulatory T-cells (Treg), (2) myeloid-derived suppressor cells (MDSC), and (3) tumor-associated macrophages (TAM). The Treg, MDSC, and TAM secrete inhibitory molecules such as transforming growth factor-β (TGF-β), interleukin-10 (IL-10) and express immune checkpoint ligands that inhibit the cytotoxic activity of T-cells and natural killer (NK)-cells, while also competing for available nutrients through metabolic competition [33,34]. Lack of immune activation (i.e., immune suppression) in the TME correlates strongly with resistance to therapy and poor patient prognosis [35].

Role of Immune Checkpoints and T-Cell Exhaustion: T-cells that are exposed to antigenic stimulation within the tumor microenvironment will develop progressive T-cell exhaustion, which is characterized by upregulated levels of inhibitory immune checkpoint molecules (e.g., PD-1, CTLA-4, and LAG-3). Immune checkpoint pathways serve to limit autoimmunity but can be exploited by tumors to limit the effect of effective immune responses [36].

While immunotherapy has greatly advanced the field of oncology, response rates to immune checkpoint inhibitors are still limited. Several host factors—including nutrition, systemic inflammation, and immune metabolic fitness—have been shown to significantly affect responsiveness to immunotherapeutic agents. Malnutrition and deficiencies related to micronutrients can cause immune exhaustion, potentially leading to lower response rates to immunotherapy [37,38].

Crosstalk between Metabolic and Immune Components in the Tumor Environment: The function of immune cells is intimately linked to their metabolic state. Immune cells that have been activated require adequate supplies of glucose, amino acids, and lipids in order to continue proliferating and to carry out effector functions. By contrast, however, the cancer cells are able to outcompete immune cells for the available nutrients, creating a microenvironment that is hostile to the metabolism and function of the immune cells [39]. Metabolic aberrations associated with cancer—including aerobiotic glycolysis, hypoxia, and oxidative stress—have also been shown to negatively impact the bioenergetics of immune cells, the production of cytokines, and the ability to exert cytotoxic effects on target cells. The deprivation of critical nutrients within the TME has resulted in reduced T-cell receptor signalling and diminished production of effector molecules, leading to a reduction in antitumour immunity overall [40]. The above findings provide compelling biological support for the development of immunonutritional approaches that restore metabolic competence to the immune system.

Following treatment, the impact of immune dysfunction on clinical outcomes: Degree of immune dysfunction associated with the treatment of cancer has direct prognostic significance. Lymphopenia/neutropenia is excellent predictors of risk of infection, need for treatment interruptions, hospitalizations, and overall survival. The immune suppression far beyond normal limits is linked to early disease recurrence and inferior response rates for both solid tumours and haematological malignancy [41,42].

Lymphocyte depletion caused by radiotherapy is now recognized as an independent predictor of poor survival, and chemotherapy-induced inflammation leads to muscle wasting, fatigue, anorexia, and cancer cachexia, all of which reduce the immune system's ability to provide protection [43,44].

The rationale for including immune supportive interventions is important because of the role immune competence plays in controlling tumors, tolerating treatment, andPROMOTING SURVIVAL. The interventions that support immune system function during cancer treatment are now considered one of the most important components of an entire oncology care plan. Nutrition, immunonutrient supplementation, and bioactive compounds that have been shown to modulate the immune system are acceptable biological methods to mitigate the decline of the immune system's ability to respond to cancer treatment [45,46]. This growing body of research provides strong evidence for supporting the integration of immunonutrition into the management of modern-day cancers.

Immunonutrition is an approach to providing nutrition through targeted delivery of certain nutrients that have the potential to impact the functioning of the immune system, the regulation of inflammatory responses, and the regulation of metabolic pathways, and therefore can influence clinical outcomes with disease processes such as cancer. While conventional nutritional support provides calories only, immunonutrition provides nutrients that are functionally active and therefore have the ability to enhance host defence mechanisms, preserve immune function, and provide a better tolerance to cancer treatment [47].

Immunonutrition is seen more and more as a supportive therapeutic approach in oncology for its ability to help decrease the immune suppression that occurs due to treatment, decrease the number of infection-related complications, enhance wound healing, and possibly improve the response to treatment and increase survival. The biological rationale for using immunonutrition as an adjunctive therapeutic approach is based on the close interrelationship among nutrition, the metabolism of immune cells, and the regulation of inflammation—each of which is severely disrupted in cancer patients [48].

The Importance of Immunonutrients for Patients with Cancer

Arginine

Arginine is an amino acid that is semi-essential (it is produced by the body) and is important for many functions involving cells of the immune system (e.g., T-cells) including the proliferation of immune cells; the production of nitric oxide; and the signalling pathways of T-cell receptors. Arginine plays a crucial role in the activation and function of cytotoxic T-lymphocytes and natural killer cells; therefore, patients with cancer typically have a deficiency of arginine because cancers consume larger amounts of it, along with metabolic stress on the patient, leading to a decreased ability of their immune systems to respond appropriately [49].

Research has indicated that arginine-enriched nutritional support has been shown to reduce infections after surgery, improve immune system function in cancer patients undergoing large surgical procedures, improve the way lymphocytes respond to stimuli and increase use of nitrogen during cancer therapy [50,51].

Glutamine

Glutamine is the most abundant amino acid in blood and is utilized as a primary energy source by many rapidly-proliferating cells [e.g., immune system (lymphocytes and macrophages)]. During the course of a person with cancer and its treatment, there is a depletion of glutamine, which results in breakdown of the immune system function, damage to the mucosal membrane, and increased risk for infections [52]. Clinical data show that supplementation with glutamine can help control mucositis caused either by chemotherapy or by radiation treatmet, may help prevent the loss of the gut barrier, and assist in recovery from a weakened immune system. Multiple randomized controlled trials report that patients with cancer receiving supplementation with glutamine had significantly higher counts of lymphocytes compared to those without, as well as decreased side effects associated with their cancer treatment. Omega-3 Fatty Acids Omega-3 PUFAs, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are very powerful agents that can reduce inflammation, and improve how well our immune system works and respond to treatment by certain actions. They can alter synthesis of eicosanoids, inhibit the production of pro-inflammatory cytokines and change the membrane composition of our immune cells and the way they communicate via signals (of all types). In patients with cancer, supplementing with omega-3 fatty acids appears to do the following: reduce overall inflammation; help preserve lean body mass; and enhance specific blood markers of immune function. Several studies involving cancer patients have demonstrated improved tolerance to treatment, lessening of cachexia, and increased quality of life for patients receiving omega-3 fatty acid-enhanced nutritional support.

Vitamins A, C, D, and E Vitamins are critical for maintaining the integrity of our immune system and managing oxidative stress.

•Vitamin A facilitates the function of epithelial barriers and the maturation of T-cells

•Vitamin C boosts how well phagocytes or white blood cells work and protects them from damage caused by oxidative stress

•Vitamin D influences both innate and adaptive immune responses and regulates inflammatory response in the body

•Vitamin E is an antioxidant and protects the membranes of our immune cells because it is fat soluble.

Cancer patients commonly suffer from deficiencies of these vitamins, which are linked to a weakened immune response, increased risk of infections, and worse overall outcomes. Clinical supplementation studies have shown that correcting these micronutrient deficiencies can improve immune function and decrease complications related to treatment; specific dosing is extremely important when utilizing these vitamins [60,61].

Zinc and selenium are two trace minerals that are required for the development of immune cells, act as antioxidants, and help regulate the activity of cytokines. Zinc is vital for proper function of the thymus gland, maturation of T-cells and for the synthesis of DNA. Selenium is a major constituent of selenoproteins (the proteins formed from selenium) that help regulate redox (oxidation and reduction) reactions and facilitate immune signaling [62]. Clinical studies show that zinc deficiency leads to impaired cell mediated immunity and increases the chances of developing an infection in cancer patients. In selected groups of patients, selenium supplementation has been associated with less chemotherapy-related toxicity, improved antioxidant status and better immune response [63,64].

Clinical Studies Support the Use of Immunonutrition in Cancer

Many clinical trials and meta-analysis demonstrate that immunonutrition (the use of nutrition specifically to improve immune function), especially formulations containing arginine, glutamine, omega-3 fatty acids & antioxidants, decreases the incidence of postoperative complications; reduces length of hospital stay; lowers incidence of infection; improves immune parameters in patients with cancer. Most frequently these benefits are seen in surgical oncology as well as patients receiving high doses of chemoradiotherapy [65,66].

Dietary Influence on Cancer Immunology

Impact of Dietary Intake on Immunomodulation in Cancer

Malnutrition and Thymic Atrophy due to Insufficient Protein & Calories (P.E.M.)

Malnutrition (P.E.M.) is relatively common (30-80%, depending on type/stage of cancer and treatment received) in cancer survivors. The result of P.E.M. is atrophy of the thymus gland, impaired proliferation of lymphocytes, decreased antibody production, and inadequate cellular-mediated immunity. This translates into increased risk for infections and complications related to treatment [68,69]. In contrast, multiple clinical studies have shown that cancer patients who are malnourished suffer from greater degrees of treatment related toxicity, longer treatment interruptions, lengthier hospitalizations, and lower rates of survival compared to adequately nourished cancer patients [70].

Effects of Cancer Cachexia on Immunity

Cancer cachexia syndrome has a complex etiology and is typified by unintentional weight loss, loss of muscle mass, chronic systemic inflammation, and metabolic derangements. In addition to resulting from increased production of pro-inflammatory cytokines (such as IL-6, TNF-α, IFN-γ), cancer cachexia will also directly inhibit the immune system and impede an individual's ability to utilize nutrients [71]. Specifically, cancer cachexia causes immune system dysfunctions, including: lymphopenia; poor T-cell responsiveness; and reduced NK-cell activity. Poor immune function resulting from cancer cachexia is highly indicative of decreased tolerance to therapy, diminished response rates to therapy, and increased mortality in patients who have solid tumors compared to patients who do not have solid tumors [72,73].

Therapeutic Impact of Good Nutrition

Patient Tolerance of Treatments

An adequate diet consisting of energy, high-quality protein, essential fatty acids, as well as vitamins and trace elements is essential for regenerating immune cells and for providing antioxidant protection for patients on cancer treatment. There is a growing body scientific data demonstrating that patients receiving appropriate food support experience fewer dose reductions and/or delays to chemotherapy or radiation treatment because they are able to tolerate the treatment better [74,75].

Infection Rates

The adequacy of a patient's diet is critical to support mucosal barriers and innate (natural) immune mechanisms. There are studies demonstrating that malnutrition increases the risk of infection due to cancer treatment; accordingly, there are many studies that demonstrate that a well-balanced diet will prevent/make much lower the incidence of infection, especially in patients receiving large amounts of chemotherapy/radiation or patients following large surgeries for his/her cancer [76].

Quality of Life

Nutrition is an important determinant of fatigue, physical functioning, and total quality of life (QoL) for patients with cancer. Studies evaluating the effect of dietary counselling and nutritional optimization have demonstrated improvements in appetite, functional capacity, and patient-reported QoL independent of response to tumor therapy [77,78].

How Indian Diets Can Help with Cancer

Traditional Indian food sources, which are nutritionally balanced, contain naturally occurring immune-supporting foods including pulses/cereal mix, fermented foods, seasonal vegetables/fruits, and antioxidant-rich plant-based foods. Unfortunately, due to treatment effects on appetite, changes in taste, and gastrointestinal toxicity, many Indian cancer patients are unable to eat enough food to avoid becoming malnourished [79].

Studies in India have determined that Indian cancer patients would benefit from culturally-specific dietary modifications, including meeting their protein needs (from pulses, dairy products, soy), ensuring sufficient intake of micronutrients, and developing anti-inflammatory dietary patterns to improve their immune function and the benefits of their cancer treatments [80].

Phytochemicals Help Support Cancer Patients' Immune Systems

Phytochemicals are plant-based bioactive compounds that have no traditional nutritional value; however, they affect a person's immune system, have anti-inflammatory properties, and have antioxidant activity. In cancer, phytochemicals are not cytotoxic agents, but they affect the body's ability to regulate immune function, signal inflammation, and interact with cancer tumors, allowing patients to achieve better treatment outcomes and maintain immune system competence [81].

Curcumin:

Source of Curcumin:

Curcumin is a polyphenolic compound derived from the rhizome of the plant Curcuma longa (turmeric), and is commonly found in traditional Indian cooking.

Immunomodulation Mechanisms: Curcumin acts on multiple pathways of inflammation and immune response by inhibiting nuclear factor Klappa b (NF-KB). It inhibits the production of proinflammatory cytokines (IL-6, TNF-al, IL-1 Beta), while at the same time increases ctyolitic T Cell and natural killer (NK) Cell activity. It also modulates immune checkpoint signalling and inhibits tumor-associated macrophage-mediated immune suppression [82,83].

Clinical and Experimental Evidence: Preclinical studies show that curcumin increases antitumor immune responses and reduces production of cytokines that suppress the immune system. Curcumin has improved clinical outcomes regarding the status of systemic inflammation, the state of antioxidant levels and the tolerance of treatment for patients with cancer in clinical trials as part of their conventional treatment [84,85].

Limitations: Dosing of curcumin varies by manufacturer and treatment duration as well as its biological availability (curcumin does not have good absorption and is rapidly metabolised), which affects curcumin's clinical performance. Due to the limitations described above, curcumin should not be viewed as a stand-alone anticancer treatment [86].

Resveratrol

Source: Resveratrol is a stilbene (polyphenol) present in many foods including red grapes, berries, peanuts and red wine.

Immunomodulation Mechanisms: Resveratrol modulates the immune response by activating sirtuin-1 (Sirt1), suppressing NF-KB signalling, reducing oxidative stress, and increasing activity of T cells and NK cells; it also balances the production of cytokines by decreasing IL-6 and TNF-alpha levels [87].

Trial Evidence: Within scientific literature attempts have linked resveratrol to immune system function, including its potential to bolster body's defense against tumor growth through enhancement of natural killer cell activity or stimulation of cytolytic T-lymphocytes via immunostimulation.

Currently Available Data (Human Safety): Unless documented use occurs in an acute, clinical trial (<25 persons per study) (publicly available); there has been not enough applicable evidence shared with the public to warrant wide-spread human use of RESVERATROL for any purpose. Green Tea Extract Components (EGCG) Source: Green tea leaves (Camellia sinensis).

Mechanisms of Action on Immune System Function: EGCg exerts immunologic activity by providing antioxidant properties, inhibiting pro-inflammatory cytokine production, modifying cell function of dendritic cells and lymphocytes and epigenetically regulating genes involved in immune response. Currently Available Data (Human Safety): Data from meta-analyses have shown a dose-dependent increase in natural killer cell activity with ingestion of ~3.5 grams daily of a green tea extract. As with RESVERATROL, however, the majority of this evidence base is limited to preclinical/epidemiological studies and lacks level 1 clinical trial data to support the safety of chronic EGCG use in humans.

Limitations: Long-term high dose supplementation may result in gastrointestinal or hepatic side effects. There are also a number of observational studies which form the basis of clinical evidence with no standardised doses established to date.[94]

Quercetin Source: A flavonoid widely found in onions, apples, berries, and leafy vegetables. Immune Modulating Mechanisms: Quercetin modulates immune responses through the inhibition of proinflammatory cytokines, the reduction of oxidative stress, stabilisation of mast cells, and enhancement of T cell and macrophage function. Quercetin also interrupts inflammatory enzymes and immune signalling cascades [95].

Experimental and Clinical Evidence: Experimental models of tumors demonstrate an enhancement of immune modulation and reduction in inflammation via quercetin. However, limited clinical studies show some promise for quercetin in reduction of inflammation as well as oxidative stress in patients treated with Standard Cancer Therapy.[96]

Limitations: Evidence is inadequate to draw any definitive conclusions regarding the effectiveness of quercetin in oncologic outcomes; however, bioavailability is variable depending on the food matrix and/or formulation of the quercetin consumed.[97]

Lycopene Source: A carotenoid most commonly found in tomatoes and tomato products. Immune Modulating Mechanisms: Lycopene can act as a potent antioxidant and positively impact the immune system through the reduction of oxidative stress, suppression of proinflammatory cytokines and promotion of gap junction communication. Lycopene also has a direct effect on immune cells through influencing signalling pathways associated with the ability of the body to suppress tumours [98].

Research Studies and Clinical Trials: Experimental and clinical studies have shown that a high intake of lycopene works to improve various immune parameters, especially lower levels of inflammation in individuals with prostate and gastrointestinal cancers [99].

Limitations: Most human research is observational in nature, making it impossible to determine individual differences in absorption from food sources affecting clinical results. Therefore, dietary sources of lycopene should not be used as a treatment but rather a supportive measure [100].

Study Implications: The current research supports theorizing the use of phytochemicals to support immune modulation by influencing inflammation, oxidative stress and/or immune competence in cancer patients. However, it is important not to misinterpret these nutrients as sources of curative benefits but

rather to utilize them according to principles associated with evidence-based nutritional and oncological intervention.

Immunonutrition During Cancer Treatment: There is considerable metabolic and immunological stress to cancer patients as a result of cancer treatment. The combination of chemotherapy and radiation creates both oxidative stress, inflammatory responses, and several other adverse reactions (such as myelosuppression and mucosal injury), all of which have great negative effects on an individual's immune system and ability to continue with treatment. Immunonutrition is helpful during active treatments because it will preserve or support immune function, decrease the amount of toxicity associated with treatment, or provide the nutrients necessary to continue treating the individual without interruption [101].

Immunonutrition in Chemotherapy

Chemotherapy-induced immunosuppression typically manifests as anaemia, neutropenia, lymphopenia and an increased risk of infection. Immunonutrition formulations containing arginine, glutamine, omega-3 fatty acids and antioxidants have shown to be of benefit to haematological and immune parameters in people receiving cytotoxic chemotherapy [102].

Clinical trials indicate that glutamine supplementation reduces the severity of chemotherapy-induced mucositis and diarrhoea by improving nutrient absorption as well as promoting immune recovery. Omega-3 fatty acids have been shown to decrease systemic inflammation and aid in the preservation of lean body mass thereby supporting immune resilience indirectly [103,104].

Observed clinical outcomes:

•Decreased severity of mucositis and gastrointestinal toxicity
•Improved haemoglobin and lymphocyte counts
•Reduced treatment interruption and dose reduction rates
•Improved chemotherapy tolerance and compliance [105]

Immunonutrition in Radiotherapy

Radiotherapy, particularly when large treatment areas are irradiated, can cause loss of lymphocytes, induce oxidative stress and damage epithelial barrier cells. Nutritional inequity during radiotherapy has been strongly correlated to increased toxicity and decreased completion rates of treatment [106]. Published evidence suggests that immunonutrition enhances antioxidant activity, decreases radiation-induced inflammation and maintains the viability of immune cells. Nutritional interventions have improved treatment tolerability levels and decreased the severity of radiation-induced mucositis and dermatitis in patients with head and neck cancers or gastrointestinal cancers who received nutritional support during their course of radiotherapy [107].

Clinical results were noted:

•No decline in absolute lymphocyte counts
•Less mucosal tissue damage due to radiation
•More frequent nutritional benefits during therapy
•Greater likelihood of completion of predetermined radiation course [108]

Immunonutrition and Concurrent Chemoradiation Therapy

Concurrent chemotherapy and radiation therapy presents unique immunologic and nutritional challenges that may result in severe mucositis, substantial weight loss, hematologic toxicity, and noncompliance with prescribed treatments. Since immunonutrition provides important synergism to the immunosuppression associated with concurrent chemotherapy and radiation, it is particularly applicable within this patient group [109].

Studies have shown that the early identification of patients requiring nutritional support (immunonutrition) during concurrent treatment with chemotherapy and radiation improves immune function, decrease treatment-related toxicities, and allow for uninterrupted treatment. Nutritionally supported patients demonstrate better weight maintenance, improved laboratory results, and fewer breaks in treatment than their non-supported counterparts [110,111].

Clinical results were noted:
•Reduced hematologic toxicities (anaemia, neutropenia)
•Increased adherence to and completion of therapy
•Reduced rates of delayed hospitalization and infection-related morbidity
•Improved overall tolerance of therapy and quality of life [112].

Clinical Perspective
The available evidence collectively demonstrates that immunonutrition enhances the host's ability to cope with cancer treatments through non-invasive methods of enhancing the patient's ability to survive or recover from cancer therapies. The greatest impact of immunonutrition is achieved when it is provided early in the course of treatment, tailored to the same type of treatment being delivered (i.e., chemotherapy) and to the individual patient's risk factors and nutritional status. Immunonutrition is not a substitute for anticancer therapies; however, it is an adjunct to anticancer therapies that can help support the delivery of anticancer therapies by maintaining both the immune system and the nutritional status of the patient [113].

Clinical Challenges and Limitations
Despite the increased awareness of immunonutrition and the use of phytochemicals in the context of treating cancer, there are several challenges to the clinical application of these therapies.

Limited Availability of Large Randomized Controlled Trials
Most of the evidence of immunonutrition and phytochemicals is derived from small-scale clinical studies, observational studies, and animal studies. There are currently very few large, well-designed, multicentre randomized controlled trials (RCTs) evaluating hard clinical outcomes such as overall survival, time to recurrence, and long-term immune function. This lack of available high-quality evidence prevents health care providers from formulating standardized clinical guidelines [114,115].

Herb–Drug Interactions
One of the biggest challenges in integrative oncology is the potential for herb–drug interactions. Several of the phytochemicals known to provide benefits in cancer patients can influence cytochrome P450 enzymes, drug transporters, and metabolic pathways, thus potentially affecting the pharmacokinetics and pharmacodynamics of chemotherapeutic agents. The under-reporting of concurrent herbal supplementation in clinical studies poses an additional challenge in assessing the risk associated with herb–drug interactions [116,117].

Quality Control and Standardization
Tremendous variation exists between herbal and phytochemical extract compositions with regard to their purity and bioactive levels. Plant diversity, growing conditions, extraction techniques and final product formulation cause this diversity resulting in myriad therapeutic outcomes due to inconsistencies between studies created through lack of standardization of product types [118].

Dosage Variability and Bioavailability
The optimal dose regimens for immuno-nutrients/phytochemicals for cancer patients has yet to be determined. Dosage will vary based on at least four factors; stage of disease, type of treatment modality, nutritional state and patient metabolic variant. In addition, many phytochemicals and their metabolites have a low level of oral bioavailability resulting in a wide variety of formulations being used with no standardization among studies [119,120].

Substantial Limitations
These limitations indicate the need to be cautious in interpreting data from available research and emphasize the necessity to incorporate immuno-nutrition into evidence-based oncology rather than using it as a sole or unmonitored treatment modality.

Future Research Directions

To increase the clinical relevance and translational implications of immuno-nutrition and phytochemicals in cancer treatment; future research efforts should include the following:

1. Multicentre clinical trials
Prior large multicentre / RCT's have been performed assessing the efficacy of using immuno-nutrition or phytochemical interventions in multiple cancer types, therapy modalities, and patient populations. These studies will need to use standard formulations of the products, as well as, definition of study end points, and collected long-term data to determine studies results in relation to survival and recurrence of cancer.

Multi-Centre Clinical Trials
To measure how effective immuno-nutrition and phytochemical treatments are for different types of cancers, different types of treatments, and in different populations, pharmacists will need to run large multi-centre RCT trials that have the same standardized formularies, endpoints that are clearly defined, and long-term follow-up to see if they improved a subject's survival or recurrence rates [121].

Biomarker Approaches and Personalization
Future clinical trials should utilize immune, inflammatory, metabolic, and nutritional biomarker evaluations to find patients who will respond to immuno-nutrition. This biomarker-based stratification will enable personalized approaches to therapy, optimizing the dosage and improving patient outcomes, as well as fewer side effects [123,124].

Looking Forward
In order to move the field of immuno-nutrition from supportive care to a precision adjunctive therapy, we will need multiple disciplines to collaborate; rigorous methodology must be utilized to enhance reproducibility; and modern oncology-based research paradigms must be embraced.

Conclusion
In the treatment of cancer patients, immunonutrition is a viable support strategy that recognizes the interactions between nutrition, immunity, inflammation, and tolerability of treatment. Evidence from experimental and clinical studies indicates that providing targeted nutritional interventions can improve the outcomes of patients in terms of reducing the toxicity of treatment, maintaining adequate immune response, enhancing adherence to treatment regimens, and enhancing the quality of life of cancer patients.
However, there is still a limited amount of data, and many findings from studies are equivocal due to differences in design, small sample sizes, lack of standardization, and absence of long-term clinical endpoints. While positive results have been reported for small clinical trials and observational studies, further large, well-controlled and randomized clinical trials will be necessary to draw definitive conclusions about the effect of immunonutrition on overall patient survival and disease control.
Immunonutrition should be considered an integrative ancillary therapy rather than a substitute for standard treatment in oncology. The main purpose of using immunonutrition is to provide an adjunct to evidence-based oncology treatment in a personalized way under clinical supervision. Future integration of this modality into standard oncology practice will require extensive high-quality data, standardized protocols, and collaborative work among different specialties within oncology for both patient safety and continued therapeutic relevance of immunonutrition.

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