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Review

# Phytotrapy of cyclophosphamide-induced immunosuppression

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ABSTRACT

Cyclophosphamide (CP) is a cytotoxic drug that can suppress both humoral and cellular immunity. Combining traditional medicinal herbs and chemotherapy drugs are used to improve immunity and quality of life performance status. In this paper, the effects of plant extracts, active components and their derivatives on immunosuppression of CP are discussed.

Appropriate keywords were used to search through PubMed, Google Scholar, and Sciverse. All relevant results published from 1990 to date were chosen for final review.

Over 50 references were found in which plant extracts, active components and their derivatives have been tested for their immune protective effects against CP-induced immune toxicity. Although there are several plants shown to be effective in animal models, no study was carried out on human subjects. According to the results; we can claim that plants and their active ingredients are good candidates for alternative adjuvant chemotherapy in reducing the immunotoxicity of CP.



*Abbreviations:* ALDH, aldehyde dehydrogenase; BMC, bone marrow cells; CD4, cluster of differentiation 4; CD8, cluster of differentiation 8; CP, cyclophosphamide; CR3, complement receptor 3; CTL, cytotoxic T lymphocytes; DLC, differential leukocyte count; DNA, deoxyribonucleic acid; DTH, delayed-type hypersensitivity; GM-CSF, granulocyte macrophage colony stimulating factor; HA, humoral antibody; Hb, hemoglobin; HT, haemagglutinating titer; IFN-γ, interferon-gama; IgG, immunoglobulin G; IgM, immunoglobulin M; IL-2, interleukin-2; IP, intraperitoneal; LBP, *L. barbarum* polysaccharides; LPS, lipopolysaccharide; MLE, Marjoram leaf aqueous extract; MLP, Marjoram leaf powder; NBT, nitroblue tetrazolium; NK, natural killer; ODPs, polysaccharides from *O. dillenii*; PFCs, plaque forming cells; PSM, polysaccharides isolated from Makgeolli; PWBC, peripheral white blood cell; QHS, quantitative hemolysis of SRBC; RBC, red blood cell; SFI, Shenqi Fuzheng injection; Spp, species; TLC, total leukocyte count; TLRs, toll-like receptors; TNF-α, tumor necrosis factor alpha; WBC, white blood cell; ZYQL, Zhuyeqing Liquor.

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## Contents



## 1. Introduction

The immune system plays an important role in the pathophysiology of other disease states such as cancer and atherosclerosis. Immunotoxicants are factors of the external environment which cause significant changes in the immune mechanisms in humans and animals. Some of the factors leading to immune suppression are stress, pesticides, alcohol and tobacco abuse, antibiotics, chemotherapy, birth control pills, cortisone, and other drug therapies (Riahi et al., 2010, 2011; Wahab et al., 2014).

CP is a cytotoxic alkylating agent with a broad spectrum of activity against a variety of diseases. CP administration causes hematopoietic depression (leukemia, lymphoma, pancytopenia), gastrointestinal (hepatoxicity, nausea, vomiting), hemorrhagic cystitis, and alopecia (Emadi et al., 2009). Immunosuppression is a major side effect of long term CP therapy in cancer patients. Body weight, relative weights of spleen and thymus, DLC (Differential Leukocyte), TLC (Total Leukocyte Count), QHS (Quantitative Hemolysis of SRBC), PFCs (Plaque Forming Cells), HA (Humoral Antibody), DTH (Delayed-Type Hypersensitivity) reaction, BMC (Bone Marrow Cells), B-cell and T-cell proliferation, and NK (Natural Killer) cell activity decreased by high doses of CP (Hussain et al., 2013). Mechanistically, CP, as a prodrug, is converted to 4-hydroxycyclophosphamide and its tautomer aldophosphamide in the liver. These compounds freely diffuse into the cell and are converted to the active compound phosphoramide mustard. It passes the nuclear membrane, binds to DNA and impedes the synthesis of nitrogenous bases and induces apoptosis in immune cells (Ho and Zloty, 1993).

Toxic effects against normal human tissues are the main dose-limiting drawback in CP therapy that confines treatment protocol and reduces quality of life. The greatest disadvantage of using synthetic immunomodulatory agents is their