



ISSN: 2348-1900

Plant Science Today

<http://www.plantsciencetoday.online>



OPEN ACCESS

Review Article

# Phytotherapy: An anti-hepatotoxicity and hepatoprotective approach in chemotherapy

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## Article history

Received: 25 February 2019

Accepted: 10 March 2019

Published: 01 April 2019

## Editor

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## Abstract

Chemotherapy induced-hepatotoxicity is one of the prevalent problems among cancer patients, with a wide spectrum of complications from liver dysfunction to liver necrosis. Therefore, in this study, we review the research findings on the effects of medicinal herbs and herbal compounds on the hepatotoxicity induced by anticancer drugs. The words hepatotoxicity and *hepatoprotective* along with the words *cancer drug* or *chemotherapy* in combination with some herbal terms such as *medicinal plant*, *phyto\** and *herb\** were used to search for relevant publications indexed in the *Institute for Scientific Information* (ISI) and *PubMed*. Available evidence shows that certain medicinal plants and herbal derivatives can reduce cancer drug-induced hepatotoxicity and protect liver cells against complications by regulating hepatic enzymes and increasing antioxidant enzyme activities. Some herbal formulations, including traditional Chinese medicine, have also been reported to exhibit such effects. Medicinal plants can exert anti-hepatotoxicity effects mainly by increasing antioxidant activity, inhibiting inflammatory processes, and reducing cell necrosis induced by anti-cancer drugs. Phytotherapy can be used as an effective complementary treatment for anticancer drug-induced hepatotoxicity and prevent various complications in the liver.

**Keywords:** Hepatotoxicity; Hepatoprotective; Medicinal herbs; Cancer drugs; Chemotherapy

## Publisher

Horizon e-Publishing Group

**Citation:** Ghanadi K, Hasanvand A, Abbaszadeh S, Heidari-Soureshjani S, Suhan T. Phytotherapy: An anti-hepatotoxicity and hepatoprotective approach in chemotherapy. *Plant Science Today* 2019;6(2):114-122. <https://doi.org/10.14719/pst.2019.6.2.514>

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**Indexing:** Plant Science Today is covered by Scopus, CAS, AGRIS, CABI, Google Scholar, etc. Full list at <http://www.plantsciencetoday.online>

## Introduction

With the spread of industrialization, cancers are one of the major causes of death in the world, with approximately 14 million new cases and 8.2 million

cancer-associated deaths in 2012 (1). Anticancer drugs may cause hepatotoxicity alone or due to interaction with other drugs, which is transient in some cases, or leads to liver tissue damage and threatens the life of the individual in other cases

(2,3). Certain classes of chemotherapeutic agents such as alkylating agents, anti-metabolites, anti-tumor antibiotics, isomerase inhibitors and mitotic inhibitors, hormone therapy and immunotherapy cause hepatotoxicity (2). Sinusoidal obstructive syndrome (SOS), steatosis, pseudocirrhosis, acute hepatitis and necrosis are conditions that correlate with liver abnormalities in patients being treated with chemotherapy and lead to abnormal liver test results (4,5). However, the hepatotoxicity mechanism is still unclear (5). Although the use of hepatoprotective agents in oncology is beneficial, no documented evidence exists for their clinical use (6). Traditional and complementary medicine (TCM) approaches (Such as aromatherapy, hypnotherapy, yoga, massage therapy, use of medicinal plants, etc.) have been used to prevention and treatment diseases (7-13), where the herbal-based medicines were the most commonly used form of TCM (14-20). They have little to no side effects compared with synthesis drugs. Various studies have shown that medicinal herbs can be effective, inexpensive, and efficient treatments for various diseases, including against toxicity (21-30). Hepatoprotective agents seem to be useful in the oncologic setting, yet they are still not widely documented for clinical usage (6). Therefore, this article reviews research findings on the effects of medicinal plants and plant compounds on anticancer drug-induced hepatotoxicity.

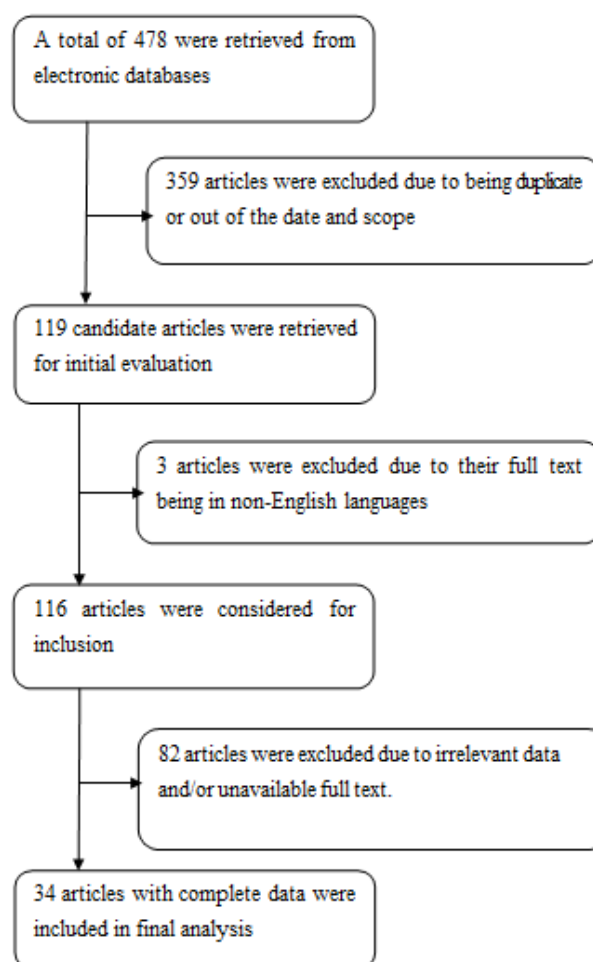
### Search strategies

The key words of interest and *Endnote* software were used to conduct this review. The key words hepatotoxicity and *hepatoprotective* along with the words *cancer drug* or *chemotherapy* in combination with some herbal terms such as *medicinal plant*, *phyto\**, and *herb\** were used to search for relevant publications indexed in the *Institute for Scientific Information* (ISI) and *PubMed* with *EndNote* software (Table 1).

A standard form was designed, which included items such as aim or the title of the study, intervention, outcome, variables, journal name, period, and number. The article's contents that were relevant to this study were recorded on the form and entered into the study upon agreement of the researchers involved in this study. Then the plants and the plant-based products that were reported to be effective to treat or reduce symptoms of cancer drug-induced hepatotoxicity were selected. The articles whose full texts were not accessible, studies with non-positive effects, non-English language articles, review articles, and studies that were not related to the purpose of this study were excluded after all researchers in this study agreement was achieved. Fig. 1 illustrates how the articles were selected for final analysis.

**Table 1:** Number of studies divided by database

Hepatotoxicity+ cancer drug+ medicinal plant	PubMed	14
	ISI	17
Hepatotoxicity+ cancer drug+phyto*	PubMed	31
	ISI	20
Hepatotoxicity+ cancer drug+herb*	PubMed	35
	ISI	47
Hepatotoxicity+ chemotherapy + medicinal plant	PubMed	4
	ISI	4
Hepatotoxicity+ chemotherapy + phyto*	PubMed	10
	ISI	5
Hepatotoxicity+ chemotherapy + herb*	PubMed	10
	ISI	16
Hepatoprotective + cancer drug+ medicinal plant	PubMed	40
	ISI	34
Hepatoprotective + cancer drug+ phyto*	PubMed	60
	ISI	29
Hepatoprotective + cancer drug+ herb*	PubMed	39
	ISI	36
Hepatoprotective + chemotherapy + medicinal plant	PubMed	4
	ISI	3
Hepatoprotective + chemotherapy + phyto*	PubMed	4
	ISI	4
Hepatoprotective + chemotherapy + herb*	PubMed	6
	ISI	6
Total	PubMed	257
	ISI	221



**Fig. 1.** Flowchart of the process of selecting the articles for final analysis

**Table 2:** Medicinal plants that have an effect on cancer drug-induced hepatotoxicity

References	Plants	Cancer drug / treatment-inducing the hepatotoxicity	Study Design	Type of administration	Main effects or mechanisms
Kumari et al. (31)	<i>Phyllanthus fraternus</i>	Cisplatin and cyclophosphamide	Experimental ( <i>in vivo</i> )	Aqueous extract	Protective effect against mitochondrial dysfunction induced by co-administration of cisplatin and cyclophosphamide and did not show any significant changes on mitochondrial membrane bioenergetics
Dkhil et al. (32)	<i>Azadirachta indica</i>	Cisplatin	Experimental ( <i>in vivo</i> )	Methanolic neem leaves extract	Reducing oxidative stress in liver by decreasing malondialdehyde and nitric oxide and improving glutathione content and glutathione-S-transferase, glutathione peroxidase (GPx), catalase, and superoxide dismutase activities.
Zarei and Shivanandapa (33)	<i>Decalepis hamiltonii</i>	Cyclophosphamide	Experimental ( <i>in vivo</i> )	Aqueous extract	Mitigating cyclophosphamide-induced oxidative stress and reversing expression of genes for antioxidant enzymes.
Zheng et al. (34)	<i>Camellia sinensis</i>	Cisplatin	Experimental ( <i>in vivo</i> )	Pu-erh tea powder	Decreasing plasma malondialdehyde and increasing the superoxide dismutase and glutathione because less use of antioxidant compounds may not affect the production and control of oxidative metabolites, or on the other hand, the excessive use of these plants and their compounds has adverse effects on the anticancer and apoptotic effects of anticancer drugs, oxidase (GSH-PX) levels and GSH-PX/MDA ratio
Huang et al. (35)	<i>Antrodia cinnamomea</i>	Cisplatin	Experimental ( <i>in vivo</i> )	Aqueous extract	Reducing cisplatin-induced hepatic inflammation and cell death.
Devi and Mazumder (36)	<i>Curcuma caesia</i> Roxb.	Cyclophosphamide	Experimental ( <i>in vivo</i> )	Methanolic extract	Causing a decrease in aspartate aminotransferase, alanine aminotransferase, and peroxidation as well as an increase in the level of endogenous antioxidants such as glutathione and glutathione reductase
El-Naggar et al. (37)	<i>Rosmarinus officianalis</i>	Cyclophosphamide	Experimental ( <i>in vivo</i> )	Methanolic extract	Lowering level of aspartate aminotransferase and lipid profile and minimizing the histological damage
Tuorkey (38)	<i>Nigella sativa</i>	Cyclophosphamide	Experimental ( <i>in vivo</i> )	Oil	Protecting DNA
Ladas (39)	<i>Silybum marianum</i>	Methotrexate, Mercaptopurine and Vincristine	Clinical trial	Capsule contain powder	Reducing serum levels of Aspartate aminotransferase (AST) and Alanine Aminotransferase (ALT) after chemotherapy
McBride et al. (40)	<i>Silybum marianum</i>	Daunorubicin and cytarabine	Case-report	Extract	Returning serum levels of AST and ALT after chemotherapy and Anaplastic lymphoma kinase (ALK) to the baseline before start of chemotherapy
Lata et al. (41)	<i>Phyllanthus fraternus</i>	Cyclophosphamide	Experimental ( <i>in vivo</i> )	Aqueous extract	Inhibition of lipid peroxidation and augmentation of endogenous antioxidants
Ahmadipour et al. (42)	<i>Zataria Multiflora</i> Boiss	Cisplatin	Experimental ( <i>in vivo</i> )	Methanolic extract	Reducing the level of AST, ALT and ALP serum activity;inhibiting lipid peroxidation and protein carbonylation;restoring antioxidant enzymes (SOD, CAT, and GSH-Px); elevating glutathione level
Tag et al. (43)	<i>Morus nigra</i>	Methotrexate	Experimental ( <i>in vivo</i> )	Ethanollic extract	Reducing activity of AST, ALT, ALP and LDH
Zhu et al. (44)	Panax (Ginseng)	Cyclophosphamide	Experimental ( <i>in vivo</i> )	Compounds, including ginsenoside	Reversing GSH metabolism and primary bile acids synthesis and NRF 2, one of the regulatory elements of the expression of GCLC, GCLM, GS, GST, NTCP and MRP3
Ettaya et al. (45)	<i>Marrubium vulgare</i>	Cyclophosphamide	Experimental ( <i>in vivo</i> )	Aqueous extract	Inhibiting lipid peroxidation, and increasing enzymatic defense system (SOD, CAT, GPx) against oxidative stress.
Sheweita et al. (46)	<i>Foeniculum vulgare</i>	Cyclophosphamide	Experimental ( <i>in vivo</i> )	Essential oils	Restoring antioxidant enzymes (SOD, CAT, GR, GST, and GPx)
Famurewa et al. (47)	<i>Cocos nucifera</i>	Methotrexate	Experimental ( <i>in vivo</i> )	Kernel oil	Increasing serum activities of oxidative stress markers (SOD, CAT, GPx and GSH) and decreasing lipid peroxidation

### **Medicinal plants, compounds and derivatives that effect cancer drug-induced hepatotoxicity**

Plants can help reduce hepatotoxicity through various mechanisms (Table 2).

There are numerous plant compounds for the treatment of chemotherapy-induced nephrotoxicity in patients that, in addition to protecting the liver against toxic substances, prevent necrosis as well. Plants can help reduce hepatotoxicity through various mechanisms (Table 3).

### **Mechanisms of hepatoprotective and anti-hepatotoxicity properties of medicinal herbs**

Phytochemicals can exert their hepatoprotective properties through essential oils, phenyl compounds, monoterpenoids, coumarins, diterpenoids, alkaloids, triterpenoids, steroids, and others. These compounds inhibit oxidative stress-inducing agents, damage to proteins and DNA, and lipid peroxidation, and therefore lead to the formation of highly immunogenic molecules, amplification of the inflammatory response, and induction of necro-apoptosis of hepatocytes. Reactive oxygen species (ROS) also contributes to the production of the TGF- $\beta$  pro-fibrogenic mediator from Kupffer cells and the circulating inflammatory cells and activates hepatic stellate cells directly, which triggers fibrosis (63). In addition to protecting the liver against anticancer drugs, medicinal plants and plant compounds can also protect the liver against other drugs (64,65) and toxic substances (66-69) by exerting their antioxidant activity. These natural treatments can also exert anticancer effects themselves by inducing growth arrest and triggering pro-apoptotic death in liver cells (70). Some plants, such as *Lindera obtusiloba*, help protect the liver through the IGF-1 and NF $\kappa$ B signaling pathways by inhibiting critical receptor tyrosine kinases that contribute to the progression of human hepatocellular carcinoma (71). In addition, treatment with phytoestrogen prevents increase in levels of malondialdehyde, nitric oxide, ALT, and AST, and increases the activity of superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase. It also increases levels of glutathione (GSH) and glutathione reductase (GR). Through such mechanisms, they protect against mitochondrial damage and cell apoptosis (32,36, 72,73). Some medicinal plants also exhibit anti-nephrotoxicity properties by inhibiting inflammatory processes (decreasing NF $\kappa$ B-mediated hepatic inflammation) and decreasing cell necrosis (35,74).

At the cellular level, it can be argued that mitochondrial damage is one of the most significant consequences due to the increase of ROS in chemotherapy, which occurs due to structural changes, increased mitochondrial permeability, and reduced mitochondria membrane, which then disrupts normal cell function (75). But despite the protective and anti-necrotic properties, certain medicinal plants or

their derivatives at high doses can cause cytotoxicity in liver cells (76,77), and in some cases, herbal self-care is used for treating these toxicities (78). Therefore, the use of medicinal plants should be supervised by a specialist and physician and special measures should be taken for patients with liver disease.

### **Complications and limitations of medicinal herb use with chemotherapy**

Anticancer drugs have major adverse effects through oxidative stress pathways, inflammatory processes, and cell apoptosis. Plants and their derivatives mainly protect the liver against free radicals and inflammatory cytokines.

They can also induce their properties by increasing the content of glutathione and modulating various signal transduction pathways (79). However, it should be noted that the use of antioxidants and even some herbal extracts for the prevention and reduction of tissue toxicities should be supervised by a physician, and that they should be taken with caution (80). Because studies show that polyphenols in green tea (as a plant with high antioxidant properties) and alkaloids and aristolochic acids in some plants can cause inflammation and nephrotoxicity, these can cause liver dysfunction and apoptosis of normal liver cells (81-84). However, because of the numerous side effects of anticancer drugs such as hepatotoxicity, bone marrow suppression, and nephrotoxicity, it is necessary to seek out alternative anti-cancer methods. This alternative method can be use of herbal (85) or chemical drugs. However, the use of antioxidant compounds with anticancer drugs is still debatable because some studies suggest that excessive use of antioxidant compounds can interfere with the process of chemotherapy and cancer treatment (86). Other studies have demonstrated the beneficial effects of antioxidants and a decrease in damage to normal cells and complications of chemotherapy by these compounds (87). Even so, interaction of anticancer drugs with herbal drugs can cause severe impairments in the patient that cause certain problems in the treatment process and the immune system, including nausea and vomiting, alopecia, fatigue, inflammation, peripheral neuropathy and pain (88), and even in some cases, hepatotoxicity in cancer patients (89). In addition, herbal medication constituents that exert hepatoprotective activity are poorly absorbed after oral administration; methods that can improve their bioavailability must be developed and active plants must be isolated (63). It is essential to determine the optimal effective dosage without toxicity in the use of these drugs, because small amounts of antioxidant compounds may not affect the production and control of oxidative metabolites, while excessive use of these plants and their compounds has adverse effects on the anticancer and anti-apoptotic effects of anticancer drugs.

**Table 3:** Medicinal plant compounds and derivatives shown to have an effect on cancer drug-induced **hepatotoxicity**

Medicinal plants compounds					
References	Herbal compounds / derivatives	Cancer drugs that induced hepatotoxicity	Study Design	Type of administration	Main effects or mechanisms
Liu et al. (48)	Traditional Chinese medicine composed of Xiao-Chai-HuTang, Huang-Lian-Jie-Du-Tang or Yin-Chen-Wu-Ling-San	Ara-C, bleomycin, carboplatin, cisplatin, cyclophosphamide, dacarbazine, doxorubicin, etoposide, fluorouracil, formoxol, gemcitabine, ifosfamide, mitoxantrone, methotrexate, mitomycin C, oxaliplatin, taxol and taxotere (with potential hepatotoxicity); arimidex, CPT-11, faslodex, herceptin, navelbine, tamoxifen, UFUR	Case-control	Extracts in the form of powders	Have protective effect by reducing serum levels of AST and ALT after chemotherapy
Gnanasekaran et al. (49)	Vivartana composed of <i>Cassia auriculata</i> (leaves), <i>Syzygium cumini</i> (seed coat), <i>Thespesia populnea</i> (bark), <i>Piper longum</i> (dried fruit)	Cyclophosphamide	Experimental ( <i>in vivo</i> )	Powder	Exert its hepatoprotective properties by regulating AST and AST
Gong et al. (50)	Chinese ZengmianYiliu granule composed of Radix Astragali Mongolic, Radix Codonopsis, Radix Rehmanniae, Herba Scutellariae Barbatae, Rhizoma Atractylodis Macrocephalae	Cisplatin	Experimental ( <i>in vivo</i> )	Ethanollic extract	Prevented the elevation of the ALT and AST levels as well as the reduction of total glutathione (T-GSH), GSH, and glutathione S-transferase (GST)
Li et al. (51)	Haoqin Qingdan consist of Artemisinin, bambooshavings, Pinellia ternata, Indian buead, Scutellaria baicalensis, Aurantii fructus, Aurantii nobilis pericarpium, and Biyu powder	Cyclophosphamide	Experimental ( <i>in vitro</i> )	Aqueous Extract	Attenuated SOD and GSH elevated levels; inhibit apoptosis by reducing cleaved caspase-3 expression
Medicinal plants compounds' derivatives					
Oyagbemi et al. (52)	Gallic acid	Cyclophosphamide	Experimental ( <i>in vivo</i> )	Herbal derivative	Led to activation of catalase and GSH-S-transferase by increasing antioxidant defense, such as elevating the level of GSH
Olayinka (53)	Gallic acid	Cyclophosphamide	Experimental ( <i>in vivo</i> )	Herbal derivative	Ameliorated against the decrease in SOD, catalase and GST activities. Also has antioxidant activity
Wu et al. (54)	Paeonol	Epirubicin	Experimental ( <i>in vivo</i> )	Herbal derivative	Inhibiting the PI3K/Akt/NF-kB pathway through 4T1-tumor bearing mice
Gao et al. (55)	Ginsenoside Rg1	Cisplatin	Experimental ( <i>in vivo</i> )	Ginseng extract	The antioxidant proteins associated with the Nrf2 signaling pathway in mice increased
Abdelmeguid et al. (56)	Silymarin	Cisplatin	Experimental ( <i>in vivo</i> )	Herbal derivative	Reversed changes in liver where most hepatocytes appeared diminutive with vacuolated cytoplasm, dilated sinusoids and organelle disorganization
Hagag et al. (57)	Silymarin	Methotrexate	Clinical trial	Herbal derivative	Reducing the level of ALT and AST and alkaline phosphatase
Olayinka et al. (58)	Quercetin	Melphalan	Experimental ( <i>in vivo</i> )	Herbal derivative	Hepatic ascorbic acid, GSH, glutathione-S-transferase, SOD, and catalase activities decreased; reestablished hepatic antioxidant status and lipid peroxidation
Schwengel et al. (49)	Resveratrol, rutin, quercetin, and quercetin nanoemulsion	Oxaliplatin	Experimental ( <i>in vivo</i> )	Herbal derivative	Reduced immunopositivity for the apoptosis marker caspase-3
Lin et al. (60)	Glutathione	Oxaliplatin	Experimental ( <i>in vivo</i> )	Herbal derivative	Serum ALT, MDA and AST level were decreased.
Mehrzadi et al. (61)	Berberine	Methotrexate	Experimental ( <i>in vivo</i> )	Herbal derivative	Serum levels of AST, MDA and ALT decreased and GSH level as well as GPx activity increased
Mir et al. (62)	Zingerone	Cyclophosphamide	Experimental ( <i>in vivo</i> )	<i>Zingiber officinale</i> derivative	Restoration of hepatic markers, amelioration of lipid profile, and improvement of antioxidant status and DNA damage

## Conclusion

Phytotherapy can be used as an effective and efficient approach to treat hepatotoxicity caused by anticancer drugs, and prevent several complications in the liver. Plants and their compounds and derivatives can protect the liver against anticancer drugs and are used as an alternative to chemical treatments mainly due to their antioxidant and anti-inflammatory properties.

However, it is necessary to develop evidence based on human studies to obtain more reliable results regarding the safety and efficacy of herbal drugs in the chemotherapy process. More research must be done to accurately determine the safety and efficacy of potential herb–drug interactions upon concurrent administration.

## Authors' contribution

SHS and SA have done the collection of literature. All authors prepared the content of the manuscript, provided inputs, and approved the final version.

## Competing Interest

The authors declare that they have no competing interest.

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