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Review Article

Concurrent administration of anticancer chemotherapy drug and herbal medicine on the perspective of pharmacokinetics

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ABSTRACT

With an increasing number of cancer patients seeking an improved quality of life, complementary and alternative therapies are becoming more common ways to achieve such improvements. The potential risks of concurrent administration are serious and must be addressed. However, comprehensive evidence for the risks and benefits of combining anticancer drugs with traditional herbs is rare. Pharmacokinetic investigations are an efficient way to understand the influence of concomitant remedies. Therefore, this study aimed to collect the results of pharmacokinetic studies relating to the concurrent use of cancer chemotherapy and complementary and alternative therapies. According to the National Health Insurance (NHI) database in Taiwan and several publications, the three most commonly prescribed formulations for cancer patients are Xiang-Sha-Liu-Jun-Zi-Tang, Jia-Wei-Xiao-Yao-San and Bu-Zhong-Yi-Qi-Tang. The three most commonly prescribed single herbs for cancer patients are *Hedyotis diffusa*, *Scutellaria barbata*, and *Astragalus membranaceus*. Few studies have discussed herb–drug interactions involving these herbs from a pharmacokinetics perspective. Here, we reviewed Jia-Wei-Xiao-Yao-San, Long-Dan-Xie-Gan-Tang, *Curcuma longa* and milk thistle to provide information based on pharmacokinetic evidence for healthcare professionals to use in educating patients about the risks of the concomitant use of various remedies.

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1. Introduction

The use of complementary and alternative medicine (CAM) has been increasing each year, particularly among cancer patients [1]. Up to 52% of cancer patients had used more than one CAM [2], and over 80% of cancer patients use CAM concurrently with chemotherapeutic agents during the initial phases of cancer treatment [3]. Moreover, approximately 50% Chinese cancer patients in North America take herbal prescriptions as assistance [4]. Breast cancer patients are the major potential users of CAM, and followed by prostate and melanoma cancer patients [5]. An interesting study revealed that the source of information on CAM use was friends in 2011 but social media in 2014 [6]. Importantly, the media encourages patients to use herbal medicine to improve their health but rarely educates consumers regarding the potential risks of concomitant use [7]. Therefore, the potential risks and benefits of coadministration of herbal remedies and conventional medicines must be considered. Given comparing the single drug with herbs, their interactions are more complicated and un-predictable than the combination of conventional medicines because of numerous components in herbs [5]. For example, St. John's wort, a notable supplementary, frequently affects the pharmacokinetics of concomitant medicines, such as indinavir, saquinavir, cyclophosphamide, docetaxel, vincristine, etoposide, and irinotecan, most of them are cytochrome P450 enzymes or p-glycoprotein substrates [8,9]. Consequently, the majority of influences are the critical concern by clinicians because the ingested herbs may impact the efficacy and safety of medicines [5]. On the other hand, only 25% cancer patients received the advices from their doctors, even worse they rarely consulted with [10]. Indeed, physicians, medical staff, friends, and families could encourage patients to divulge the daily supplements that they are using. Then, physicians and pharmacists could provide the patients with appropriate information. This review aimed to collect relevant publications and provide medical staff with pharmacokinetics concepts.

2. Strategies of traditional Chinese medicine for cancer patients

Cancer was documented in ancient medical literature as cancerous tissue shaped like a hard stone with a lumpy surface [11]. The first cancer-related record is in an ancient medical book, Huangdi Neijing, which described cancer as a gathering into a permanent massive tumescence [11]. Furthermore, Hau Tuo, the phenomenal Oriental doctor practicing Chinese medicine in the 2nd century, suggested that cancerous lesions located in the internal body should be removed from an anesthetized patient by surgery [12]. Additionally, cancer characteristics, the frequency of lesions in various locations, and sex-specific variations in cancer were recorded in ancient literature. For example, cancer is a lesion that grows deep, similar to a cave, and lesions are typically near one another: cancer is more likely in the abdomen in males, whereas the breast is a highly probable location in females. These ideas were documented in the cancer occurrence section of Ren Zai Zhi Shi Fu Yi Fang Lun, written by Shiying Yang.

Given this evidence, cancer has been recorded since the Han dynasty; therefore, cancer has affected human health for over two thousand years. The aim of traditional Chinese medicine is treatment with syndrome differentiation and personalized medicine. Hence, the determination of a suitable strategy for a specific patient depends on the pulse condition and external expression. Chinese medicine doctors have been fighting a long way against cancer with the hope of curing cancer patients, and ancient doctors compiled and documented treatment experiences. These doctors then posited five strategies: nourishing yin and enriching fluid production, clearing heat and detoxication, activating circulation and dissolving stasis, strengthening healthy energy, and combat poison with poison [11,12]. From the modern medicinal perspective, the purpose of nourishing yin and enriching fluid production is to reduce the adverse effects of chemotherapy and radiotherapy, such as nausea, vomiting, mouth ulcers, decreased saliva secretion, oral thurst, dry and painful pharynx, low body temperature, night sweats, and diarrhea, are the exterior syndrome of yin deficiency according to the traditional Chinese medicine theory. Thus, for patients suffering from adverse effects, doctors would focus on reducing the aggravating symptoms and helping them complete their chemotherapy. Some herbs with these benefits are Maidong (*Ophiopogon japonicas*), Shihu (*Dendrobium nobile*), Dangshen (*Codonopsis pilosula*), Xuanshen (*Scrophularia ningpoensis*) and Danshen (*Salvia miltiorrhiza*) [11,12]. Once the cancer grows too fast and large, it stresses the blood flow surrounding tissues. The strategy for this situation is activating circulation and dissolving stasis, as suggested by the literatures [11,12]. Safflower, Danshen, and Chuanxiong (*Ligusticum chuanxiong*) improve circulation, dissolve stasis, inhibit cancer cell proliferation, and reduce the size of the lesion [11,12]. However, if the lesion ulcerates, produces tissue fluid, and causes serious inflammation with pain, the strategy would shift to clearing heat and detoxication. The most common herbs with the ability to clear heat and detoxify are *Taraxacum mongolicum*, *Tripterygium wilfordii*, *Scutellaria barbata*, and *Hedyotis diffusa*, which are also considered against anticancer agents based on clinical studies. The ancient Oriental doctors believed that cancer poisons organs and the body, so they used extreme ways to kill cancerous tissues, such as the use of poison herbs in combating poison. Finally, the most common strategy of traditional Chinese medicine for treating cancer is strengthening healthy energy. This strategy aims to improve a patient's energy and body function and involves tonifying qi before or after cancer therapy by taking ginseng, Huangqi (*Astragalus membranaceus*), and Angelica root (*Angelica sinensis*) [11,12].

3. Contributing factors in herb–drug interactions

Concomitant treatment has an increasing tendency to reduce adverse effects, strengthen immunity, and improve general health, but the potential effects can be positive, negative or neutral when considering the simultaneous use of herbal

remedies. These potential effects result from interactions between anticancer drugs and herbs; components of the herb might affect drug-metabolizing enzymes and transporters that engaged in the metabolism and disposition of the anticancer drug. The contributing factors in herb–drug interactions from a pharmacokinetics perspective include the cytochrome P450 enzyme family [13], which is implicated in phase I reactions; glucuronidase and sulfatase, which are associated with phase II reactions; and P-glycoprotein, a drug-efflux transporter. CYP3A4, CYP3A5, CYP2D6, and CYP2C19 are vital members of the CYP superfamily [14], and they metabolize various drugs. CYP2C19 is responsible for the metabolism of numerous routinely administered drugs, including diazepam, omeprazole, S-mephenytoin, and antimalarial biguanides [15]. CYP3A4, CYP2C9 and CYP2D6 constitute approximately 50%, 18%, 2–4%, respectively, of the total CYP protein content in human liver microsomes [16,17]. Even though CYP2D6 is the least populous of these three enzymes, it is involved in metabolizing over 20% of all clinically administered drugs, particularly tricyclic antidepressants, serotonin reuptake inhibitors, and beta-blockers [17]. For example, tamoxifen is used to treat ER-positive breast cancer; this prodrug is metabolized into its active metabolites, 4-hydroxytamoxifen and endoxifen, by various CYPs, but CYP2D6 is the rate-limiting enzyme [18]. Thus, the concurrent use of a CYP2D6 inhibitor could increase the plasma levels of CYP2D6 substrates, leading to toxicity if the plasma level is greater than the therapeutic level. Such inhibitors and substrates might be components of herbs and clinical drugs, so the potential interactions are dependent on the involved enzymes. For instance, in vitro studies showed that silibinin, silymarin, and ginsenoside Rd are CYP3A4 inhibitors [19–21]; in an in vivo study, oleanolic acid, a common component isolated from plants, induced the activity of CYP2E1 [20]; emodin, a major active component in Dahuang, enhanced the activity of CYP1A1 [20]; and gallic acid, an abundant ingredient found in a variety of land plants, reduces CYP3A4 activity [20]. There is substantial evidence that various natural constituents are potential critical factors in the metabolism of drugs.

The gastrointestinal cell membranes are the main barrier of drug permeation, which related to two movement types, including passive diffusion mainly depending on the gradient between intracellular and intercellular drug concentrations and active diffusion requiring energy to move drug against an opposing concentration gradient. However, efflux transporters engaging in pumping drugs out of cell, attribute to removing metabolic end products and xenobiotic substances. Drug transporters are another contributing factor in herb–drug interactions. Most the clinically administered drugs are taken orally, so the first obstacle they must overcome is absorption through the intestine wall. ABC transporters, which are ubiquitous membrane-bound transport proteins, engage in various processes that affect pharmacokinetics such as absorption, distribution, and elimination [22]. P-glycoprotein (P-gp), located on the surface of epithelial cells, is a cellular efflux protein that pumps out numerous chemotherapeutic agents. P-gp is responsible for the efflux of harmful materials from cells of various organs, which protects the brain from xenobiotic exposure [23]. Generally, P-gp engages in removing cationic and neutral drugs, most medicine belonged to [24,25]. For anionic drugs, ABCC2/MRP2 is modulator [24,25]. Capsaicin, a major ingredient of red chili pepper, *Capsicum annuum*, is a p-gp modulator, which increases the accumulation of daunorubicin in in vitro study [26]. Other compounds as resveratrol, curcumin and 6-gingerol additionally have a similar effect on reducing drug efflux by the inhibition on p-gp activity [26]. Certain tumor cells overexpressing a series of efflux transporters are observed to be resistant to specific anticancer drugs [24,25]. The human ATP-binding cassette transporters ABCG2 (Breast Cancer Resistance Protein, BCRP) have been clarified to reduce net absorption of doxorubicin [27]. Beyond efflux transporters, influx transporters also have been recognized as a powerful influence on ADME [28]. For instance, for hepatic and renal uptake, respectively, are organic anion transporting polypeptides (OATP), OATP1B1 and OAT3 [24,25,28]. OATP1B1, OATP1B3 and OATP2B1 expressed on hepatic sinusoidal/basolateral membrane facilitate the liver uptake, but MRP1, MRP3, MRP4, MRP5 and MRP6 modulate the liver efflux [28]. Expressed P-gp, MRP2, BCRP, and BSEP on apical/canalicular membrane dominate biliary excretion [28]. In brief, some natural compounds and drugs influence both CYP enzymes and transporters; therefore, in this situation, physicians must pay careful attention to avoid concurrent use of such substances.

4. Concurrent use of traditional Chinese formulations and cancer chemotherapy

There have been several Taiwanese population-based cohort studies on prescribed traditional Chinese medicine for the treatment of various types of cancer reporting the top ten traditional Chinese medicine formulations and single herbs, of which the top 5 are listed in Table 1 [29–32]. Even though *H. diffusa* is top 1 regarding concurrent use in colon cancer, breast cancer and hepatocellular carcinoma, investigations on herb–drug interactions are limited. Xiang-Sha-Liu-Jun-Zi-Tang always occupies the top 1 or 2 places on these lists, but studies of this formulation are limited. Jia-Wei-Xia-Yao-San is frequently administered concurrently with chemotherapy in cancer patients; therefore, herb–drug interactions between Jia-Wei-Xiao-Yao-San and chemotherapeutic agents are described in the following section. In addition, *Curcuma longa* and milk thistle are commonly investigated substances, and they are discussed in section 5.1.

4.1. *Jia-Wei-Xiao-Yao-San*

Jia-Wei-Xiao-Yao-San (JWXYS) is composed of ten herbs, including Radix Angelicae Sinensis (Dang-Gui), Rhizoma Atractylodis Macrocephalae (Bai-Zhu), Radix Bupleuri (Chai-Hu), Poriae Cocos (Fu-Ling), Radix Paeoniae Alba (Bai-Shao), Radix Glycyrrhizae Uralensis (Zhi-Gan-Cao), Cortex Moutan Radicis (Mu-Dan-Pi), Fructus Gardeniae (Zhi-Zi), Rhizoma Zingiberis Recens (Wei-Jiang), and Herba Menthae (Bo-He) [33]. JWXYS has been associated with relieving climacteric syndrome, anxiety, dyspepsia, and insomnia, and some of these psychological issues are observed in cancer patients; therefore, JWXYS is one of the top three prescribed formulations for breast cancer and gastric cancer patients in Taiwan.

Table 1 – Top 5 single herbs and formulas prescribed for treating various types of cancer in Taiwan.

	Colon cancer with chronic hepatitis [24]	Colon cancer [25]	Breast cancer [26]	Hepatocellular carcinoma [23]
Single herbs				
1	*Hedyotis diffusa*		*Hedyotis diffusa*	*Hedyotis diffusa*
2	*Scutellaria barbata*		*Scutellaria barbata*	*Rhizoma rhei*
3	*Astragalus membranaceus*		*Taraxacum mongolicum*	*Scutellaria baicalensis*
4	*Atractylodes macrocephala*		*Salvia miltiorrhiza*	*Astragalus membranaceus*
5	*Salvia miltiorrhiza*		*Ziziphus spinosa*	*Salvia miltiorrhiza*
Formulas				
1	Xiang Sha Liu Jun Zi Tang	Xiang Sha Liu Jun Zi Tang	Jai Wei Xiao Yao San	Ping Wei San
2	Jai Wei Xiao Yao San	Shen Lin Bai Zhu San	Xiang Sha Liu Jun Zi Tang	Xiang Sha Liu Jun Zi Tang
3	Bu Zhong Yi Qi Tang	Bu Zhong Yi Qi Tang	Gui Pi Tang	Xiao Chai Hu Tang
4	Shen Lin Bai Zhu San	Ban Xia Xie Xin Tang	San Zhong Kui Jian Tang	Jia Wei Xia Yao San
5	Ping Wei San	Jai Wei Xiao Yao San	Bu Zhong Yi Qi Tang	Gan Lu Yin

Paclitaxel, a well-known cancer chemotherapy agent, has been approved for the treatment of non-small cell lung cancer, breast cancer, and pancreatic cancer since 2005 in the United States. Additionally, paclitaxel is approved as a first-line therapy for metastatic breast cancer and has been likely administered with JWXYS in Taiwan; therefore, an investigation of the impact of JWXYS during coadministration with paclitaxel from a pharmacokinetic perspective is valuable for providing information for clinical users. Hou et al. studied the herb–drug interactions of JWXYS and paclitaxel in rodent species [34], and reported that the plasma AUC of paclitaxel in the paclitaxel alone group was approximately 1.5-times higher than that in the group that received oral JWXYS daily for seven days and a single dose of paclitaxel. Furthermore, after pretreatment with JWXYS for seven days, the half-life of paclitaxel increased from 73 min to 111 min, and the clearance increased approximately 1.4-fold compared to paclitaxel alone [33]. Interestingly, JWXYS rarely affected the lymphatic absorption rate or the lymphatic distribution, but it influenced the metabolic enzymes and intestinal absorption, resulting in an obvious reduction in plasma paclitaxel levels [34].

Another common drug for the treatment of colorectal cancer that is likely combined with traditional herbal medicine is 5-fluorouracil (5-FU) [33]. The literature on the interaction of JWXYS and 5-FU suggests no significant difference between the concomitant or single-agent use of these two drugs in terms of pharmacokinetic parameters such as AUC, CL, and C_{max}, yet the residence time of 5-FU was prolonged after coadministration [33]. Interestingly, in the coadministration group with the high dose of JWXYS (2400 mg/kg), the free form of 5-FU was increased in the brain, but the ratio of penetration was not significantly different [33]. Regarding the pharmacokinetic parameters of 5-FU in the brain, the half-life shifted from 31.9 min to 47.2 min, and the clearance decreased from 120.0 mL/min per kg to 82.9 mL/min per kg [33], which indicated that the elimination rate of 5-FU from the brain decreased after daily pretreatment with JWXYS for five days. JWXYS is a mixture of complex compounds that might be capable of suppressing P-gp activity in the brain; thus, 5-FU accumulated in the brain because P-gp was inefficient at removing 5-FU from brain cells. This result implies that the "chemo-brain" symptom caused by 5-FU might worsen upon concomitant administration with JWXYS.

4.2. *Long-Dan-Xie-Gan-Tang formulation*

Long-Dan-Xie-Gan-Tang (LDXGT) comprises *Gentiana scabra* (Long-Dan-Cao), *Scutellaria baicalensis* (Huang-Qin), *Gardenia jasminoides* (Zhi-Zi), *Alisma orientalis* (Ze-Xie), *Clematis montana* (Mu-Tong), *Plantago asiatica* (Che–Qian-Zi), *A. sinensis* (Dang-Gui), *Rehmannia glutinosa* (Shu-Di-Huang), *Bupleurum chinense* (Chai-Hu), and *Glycyrrhiza uralensis* (Gan-Cao) and is one of the top 10 most prescribed Chinese herbal formulas for the treatment of chronic hepatitis in Taiwan [35]. Anti-inflammatory, anti-bacterial, anti-allergy, and hepatoprotective properties of LDXGT have been reported [36,37]. Gentiopicroside, geniposide, and baicalin are the major bioactive compounds within LDXGT [36,38] and are isolated from Long-Dan-Cao, Zhi-Zi, and Huang-Qin, respectively [37]. This potentially hepatoprotective formulation is potentially used concurrently with the multi-kinase inhibitor sorafenib. Ting described the herb–drug interactions of LDXGT and sorafenib in rats and revealed that no significant difference in the AUC of sorafenib with or without LDXGT [35], which suggested that the pharmacokinetic interaction of LDXGT and sorafenib might be weak at the dosage used in this study. Furthermore, AST and ALT levels and histopathological examinations to assess liver function during coadministration of LDXGT and sorafenib indicated the safety of concomitant use. The study by Ting found no significant variation in AST and ALT levels with or without LDXGT, but the histopathological examination showed inflammation in hepatocytes after short-term sorafenib treatment and hepatotoxicity after long-term treatment, yet concurrent use with LDXGT did not elicit the hepatotoxic phenomenon [35]. In conclusion, the concurrent use of sorafenib and LDXGT in the therapeutic dose range might be safe according to the pharmacokinetic and pharmacodynamic evidence, but more clinical evidence is required to prove its safety in humans.

5. Concurrent use of signal herbs and cancer chemotherapy

5.1. *Curcuma longa*

C. longa, belonging to the Zingiberaceae family, is widely cultivated in Asian countries and is used as a flavoring agent worldwide [39]. It is not only a flavoring agent but also an

herbal medicine clinically used in anti-inflammatory, antioxidative, anti-arthritic, anti-amyloid and anticancer treatments [39,40]. Its wide array of biological and pharmacological properties is attributed to its major active component, curcumin, a lipophilic polyphenol [40]. Curcumin influences various kinases and caspases to modulate multiple signaling pathways that suppress cancer [41]. For instance, curcumin suppresses nuclear factor-κB (NF-κB), thus reducing the expression of NF-κB downstream target genes, which inhibits the proliferative ability of various cancer cell lines, such as SFC-7901, MCF-7, MDA-MD-231, and MDA-MD-468 cells [42,43]. Recently, some researchers issue that curcumin and its derivatives are typified as pan-assay interference compounds (PAINS) meaning these compounds interfere with promiscuous biological targets without extraordinary impact to specific target [44,45]. Although this disadvantaging statement has claimed, a lots new drug development scientists are confidant and constantly modify these curcuminoids to improve their bio-abilities.

From the perspective of pharmacokinetics, the bioavailability of curcumin is extreme low, less than 1% [46,47], implying its absorption is weak through the gastrointestinal system. The half-life of curcumin is less than 5 min [46,47] that infers its rapid metabolism causing by glucuronidation and sulfation in liver according to Hsieh's investigation [48]. The chemical structure of curcumin has crucially readout its poor pharmacokinetics. The keto–enol tautomerization of curcumin results from the β-di-ketone moiety that leads the preferable structure is enol tautomer because a planar forms intramolecularly hydrogen-bonded structure [49], but this enol form degrades rapidly at the neutral environment within approximately 20 min, even worse at the body temperature being shorten to 10 min [50]. Therefore, these evidences reveal that curcumin is probably unstable and rapid degradation in creature bodies, or producing its metabolites, glucuronides, sulfates of curcumin and demethoxycurmin due to its instantly significant diminishing the curcumin level in blood. Taken together, these metabolites might be the main matter to contribute the multi-bioactivity of curcumin.

With the concern about herb–drug interaction, cytochrome P450 family and drug transporters are mostly considerable factors to evaluate the medicinal pharmacokinetic impact by concurrent herbs. In vitro studies showing that curcumin inhibited CYP3A4 [51], yet in vivo study associated with curcumin-induced interference indicates that curcumin activates CYP3A4 due to the fact that curcumin markedly reduces the AUC of everolimus, a macrolide immunosuppressant and a CYP3A4 substrate [48]. However, it is a dilemma to classify the ability of curcumin on CYP3A4. A considerable thesis demonstrated that the level of CYP3A4 activity modulated by curcumin serum metabolites is more activated than that by curcuminoid free form [48], so that curcumin serum metabolites comprehensively dominate the pharmacokinetics of curcumin during concurrently dosing with medicines.

Curcumin inhibits the activity of multidrug resistance (MDR) transporters, P-gp, MDR-1, and mitoxantrone resistance protein (ABCG2) [52], which might affect the pharmacodynamics of various drugs. Thus, when curcumin is co-administered with drugs with a narrow therapeutic index, the level of such drugs could increase beyond the therapeutic window, causing extremely unfavorable side effects. Recently, a study investigated curcumin and doxorubicin co-delivery because of the beneficial effects on antitumor activity and the ability to diminish the adverse effects of doxorubicin [53,54]. Ma reported a comparison of single-agent and combination treatments and showed increases in the AUC and half-life of doxorubicin upon concurrent administration with curcumin [40]. Curcumin decreases ATP-binding cassette drug transporter activity; thus, the authors concluded that this herb–drug interaction enhanced the absorption of doxorubicin and reduced the drug efflux of doxorubicin [40].

As aforementioned, we can conclude that curcumin inhibits the P-gp and CYP3A4 activities in vitro, but activates CYP3A4 and suppresses P-gp abilities in vivo. Zhang's study clearly pointed out that curcumin modulates CYP3A4 depending on its locations, for instance, curcumin enhances the CYP3A4 protein level in liver and kidney, nor in intestine [55]. Similar phenomenon of P-gp modulation is observed because curcumin enhances the hepatic P-gp protein level and reduces the intestinal P-gp protein level [55]. Therefore, on the basis of the presence of differential regulatory mechanism for protein expression, curcumin simultaneously suppresses the intestinal P-gp and CYP3A4 and up-regulates the hepatic P-gp and CYP3A4 in rodent animals, but curcumin rarely dominates these proteins immediately after oral intake signal dose. Continuous oral administration of curcumin may affect the pharmacokinetics of co-administered medicines. Consequently, cancer patients with concomitant remedies should be aware about the potential risks of the long-term using with curcumin.

5.2. *Milk thistle*

Silybum marianum L., also called milk thistle, is a remarkable hepatoprotective herb according to ancient literature, which documented its robust ability to clear obstructions of the liver and spleen [56]. Silymarin consists of a series of flavonolignans, including silibinin (silybin A and silybin B), isosilibinin, silydianin, silychristin, isosilybin A, and isosilybin B, that account for 65–80% of milk thistle extract [57,58]. Silymarin and other flavonolignans are responsible for the clinical activity against various liver diseases, including viral hepatitis, chronic hepatitis, alcoholic liver disease, cirrhosis, and toxic liver damage; the content of silibinin has been used as the major quantitative assessment of silymarin [58,59]. An in vitro study showed that silymarin modulates the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway to regulate DNA translation and transcription in the epidermal A431 cell line [60]. Silymarin induces apoptosis and cell cycle arrest in human colon cancer HT-29 cells; Agarwal reported that silibinin up-regulates the cyclin-dependent kinase inhibitors Kip1/p27 and Cip1/2, which may cause the anti-proliferative effects [61]. Silybins regulate cell cycle kinases; specifically, they activate Kip1/p27 and inhibit cyclins and CDKs to halt the cell cycle in the human hepatocellular carcinoma Hep3B and HepG2 cell lines [62]. Moreover, in vitro and in vivo studies showed that silibinin regulates the TRAIL death receptor apoptotic signaling pathway, which is the extrinsic apoptotic pathway, by

simultaneously upregulating DR5, caspase-3, and caspase-8 and downregulating MMP-7 and MMP-9, thereby inhibiting the orthotopic growth of hepatocarcinoma Hep-55.1 C cells [63,64].

Silymarin, which has limited water solubility, exhibits low oral bioavailability in humans and rats due to inefficient intestinal absorption and high first-pass phase II metabolism [65]. The glucuronide and sulfate conjugates of silibinin (silybin A and B) account for approximately 90% and 98% of the total amount of silibinin in blood and bile of humans and rats, respectively [66]. Briefly, after humans ingest silymarin, it rapidly reaches the maximum concentration within two hours and is eliminated in the free form with a half-life of 1–3 h [59,67]. Silymarin is absorbed from the intestinal tract into circulation, and phase II metabolism dominates in changing the free form to the conjugated form by glucuronidation and sulfation. Then, conjugated silymarin metabolites are excreted in bile and urine [59,67]. Therefore, silymarin conjugates, in particular glucuronides, rapidly appear in the plasma.

In an in vitro study, silymarin increased the accumulation of daunomycin in Caco-2 cells, which revealed that silymarin affects P-gp-mediated efflux [68]. Wu et al. studied changes in the pharmacokinetics of silibinin in normal rats and those with cirrhotic livers. The liver function might differ in these two groups of animals; thus, enzymatic and P-gp activities would influence silibinin metabolism. For example, the activities of sulfotransferase, acetyltransferase, glutathione transferase, and thiomethyltransferase are decreased in liver disease [59]. As shown by a previous study, silibinin underwent considerable hepatobiliary excretion, but coadministration with the P-gp inhibitor cyclosporine decreased hepatobiliary excretion, and the total silibinin level in plasma increased, revealing that silibinin is a substrate of P-gp with a competitive binding relationship with cyclosporine [59,67]. The free form of silibinin in plasma and the biotransformation ratio (AUC_{blood}/AUC_{bile}) were reduced in rats with liver cirrhosis. Wu et al. concluded that the clearance of silibinin conjugates was reduced due to extrahepatic biliary obstruction, and the activity of enzymes involved in silibinin metabolism was reduced [59,67].

Several in vitro studies have suggested that milk thistle (silymarin, silibinin, and other flavonolignans) regulates the activity of various cytochrome P450 isozymes (e.g., CYP3A4), UDP glucuronosyltransferase isoform 1A1 (UGT1A1), and ABC transporters (e.g., ABCB1 and P-gp) [69,70]. The results of phase II clinical trial of the concurrent administration of milk thistle and irinotecan in six colon cancer patients revealed no significant effect on the pharmacokinetics of irinotecan [69,70]. Other publications state that milk thistle (silymarin, silibinin, and others) has no clinical effect on CYP3A4 [70,71] CYP1A2, CYP2D6, or CYP2E1 activity [72] and does not interfere with P-gp activity [73]. Some ongoing clinical trials are evaluating combinations of silibinin or silymarin with molecular targeted therapy for hepatocellular carcinoma (HCC), such as sorafenib, but the results of these studies are rarely published. However, the available data imply that the concurrent administration of sorafenib and silibinin is a new option for HCC therapy because silymarin can protect hepatocytes and exhibit antiproliferative activity. Nevertheless, numerous silymarin products have been marketed worldwide, and these are probably meant to be taken with chemotherapy agents by HCC patients. The risk assessment of this combination therapy is critical for providing valuable information to physicians, medical staff, and patients. As discussed previously, laboratory evidence suggests that silymarin and silibinin might have benefit against several types of cancer, but their clinical activity upon coadministration with cancer chemotherapy from a pharmacokinetic viewpoint is unclear. Importantly, the results of rodent studies and clinical studies have yielded opposite conclusions, and therefore, the data are insufficient to recommend the concurrent use of milk thistle and cancer chemotherapy drugs.

6. Conclusion

Chinese medicine provides an alternative to reduce the side effects of cancer chemotherapy. Modern medical technology and knowledge must be used to clarify the risks and benefits of potential herb–drug interactions upon concurrent administration. According to the pharmacokinetics evidence described above, several natural compounds and herbs have inhibited or induced CYP enzymes in rodent studies and in vitro studies with no response in clinical trials; thus, patients must be encouraged to use CAM wisely. Although pharmacokinetics has a considerable impact that we should consider, pharmacodynamics should also be taken into consideration. Additionally, liver, kidney, and intestinal function differs in cancer patients and healthy people, and these variations should be addressed in assessments. In conclusion, the goal is to use herbs concurrently within the safe dosage range to achieve positive results after consulting physicians and pharmacists.

Conflicts of interest

The authors declare no conflicts of interest.

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