HERB-DRUG INTERACTIONS IN CANCER TREATMENT: A SYSTEMATIC REVIEW

CHOW LEE FUN

DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE (HEALTH TOXICOLOGY)

ADVANCED MEDICAL AND DENTAL INSTITUTE
UNIVERSITI SAINS MALAYSIA

2019
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2019
DECLARATION

I hereby declare that this research was sent to Universiti Sains Malaysia (USM) for the degree of Master of Science in Health Toxicology. It has not been sent to other universities. With that, this research can be used for consultation and photocopied as reference.

Sincerely,

____________________

CHOW LEE FUN

(P-IPM0036/18)
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# TABLE OF CONTENTS

DECLARATION.......................................................................................................................... ii

ACKNOWLEDGEMENT........................................................................................................... iii

TABLE OF CONTENTS.............................................................................................................. iv

LIST OF TABLES .................................................................................................................... vi

LIST OF FIGURES .................................................................................................................. vii

LIST OF SYMBOLS ................................................................................................................ viii

LIST OF ABBREVIATIONS .................................................................................................... ix

ABSTRAK ................................................................................................................................. xi

ABSTRACT ............................................................................................................................... xiii

CHAPTER 1 INTRODUCTION.................................................................................................. 1

1.1 Background .......................................................................................................................... 1

1.2 Problem statement .............................................................................................................. 2

1.3 Significance of the study .................................................................................................... 2

1.4 Objectives of the study ........................................................................................................ 2

CHAPTER 2 LITERATURE REVIEW ....................................................................................... 4

2.1 Systematic review ............................................................................................................... 4

2.2 Herbs ................................................................................................................................ 6

2.3 Anti-cancer drug ................................................................................................................. 8

2.4 Herb-drug interaction ......................................................................................................... 10

2.5 Pharmacokinetic interactions ........................................................................................... 11

2.6 Mechanism of Pharmacokinetic HDI .............................................................................. 14

2.6.1 Efflux transporter ........................................................................................................ 14

2.6.2 Influx transporter ......................................................................................................... 16

2.6.3 Cytochrome CYP 450 .................................................................................................. 17
CHAPTER 3 Methodology .................................................................................. 20
  3.1 Identification ............................................................................................. 20
  3.2 Screening .................................................................................................. 21
  3.3 Eligibility .................................................................................................. 22
  3.4 Inclusion .................................................................................................. 22

CHAPTER 4 RESULT AND DISCUSSION ......................................................... 23
  4.1 Number of studies ..................................................................................... 23
  4.2 Pharmacokinetic studies ........................................................................ 25
  4.3 Study design of pharmacokinetic studies ............................................. 44
  4.4 Type of cancer studies ........................................................................... 45
  4.5 Type of herb studies ............................................................................... 46
  4.6 Type of anti-cancer drug studies ............................................................. 47

CHAPTER 5 CONCLUSION AND RECOMMENDATIONS .......................... 49
  5.1 Conclusion .............................................................................................. 49

REFERENCES ................................................................................................. 51
LIST OF TABLES

Table 4.1 Pharmacokinetic (PK) studies of herb drug interaction............................26
Table 4.2 Pharmacokinetic studies based on action on Cytochromes CYP450
   (CYPs) metabolism .........................................................................................42
Table 4.3 Type of herb studies .................................................................................46
Table 4.4 Type of anti-cancer drug studies .................................................................47
LIST OF FIGURES

Figure 2.1 Different phases of a systematic review (adapted from Liberati et al., 2009). .................................................................6

Figure 2.2 Summary of HDI based on pharmacokinetic and potential outcome (adapted from Tarirai et al., 2010).................................12

Figure 2.3 Measurement of pharmacokinetic parameter..................................................13

Figure 3.1 Stages of systematic review process.................................................................20

Figure 4.1 Scheme of the data selection process.................................................................23

Figure 4.2 Number of journals related to herbal-drug interaction which were published from year 2008 to January 2019.............................25

Figure 4.3 Percentage of articles in pharmacokinetic interaction.................................38

Figure 4.4 Study design of pharmacokinetic studies.........................................................44

Figure 4.5 Type of cancer studies Jan 2008 – Jan 2019.....................................................46
# LIST OF SYMBOLS

- No mentioned in the study

↑ Induced or increased

↓ Inhibited or decreased

↔ No change

$T_{1/2}$ Half-life
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC</td>
<td>ATP-binding cassette</td>
</tr>
<tr>
<td>ABCG2</td>
<td>ATP-binding cassette super-family G member 2</td>
</tr>
<tr>
<td>ADME</td>
<td>Absorption, distribution, metabolism and excretion</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under curve</td>
</tr>
<tr>
<td>Bax</td>
<td>BCL2-associated X protein</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>B-cell lymphoma 2</td>
</tr>
<tr>
<td>Bcl-xL</td>
<td>B-cell lymphoma-extra large</td>
</tr>
<tr>
<td>BCRP</td>
<td>Breast cancer resistance protein</td>
</tr>
<tr>
<td>CAM</td>
<td>Complementary alternative medicine</td>
</tr>
<tr>
<td>CI</td>
<td>Clearance</td>
</tr>
<tr>
<td>Cmax</td>
<td>The maximum or the highest drug concentration in plasma</td>
</tr>
<tr>
<td>CYP</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DOAJ</td>
<td>Directory of Open Access Journal</td>
</tr>
<tr>
<td>EGCG</td>
<td>Epigallocatechin-3-gallate</td>
</tr>
<tr>
<td>EGFR-TK</td>
<td>Epidermal growth factor receptor-tyrosine kinase</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GLOBOCAN</td>
<td>Global cancer statistics</td>
</tr>
<tr>
<td>HDI</td>
<td>Herb-drug interaction</td>
</tr>
<tr>
<td>HPLC</td>
<td>High-performance liquid chromatography</td>
</tr>
<tr>
<td>Ka</td>
<td>absorption rate constant</td>
</tr>
<tr>
<td>LC-MS</td>
<td>Liquid chromatography tandem mass spectrometry</td>
</tr>
<tr>
<td>MCF-7</td>
<td>Michigan Cancer Foundation-7</td>
</tr>
<tr>
<td>MDR1</td>
<td>Multi-drug resistance protein 1</td>
</tr>
<tr>
<td>mRNA</td>
<td>Messenger RNA</td>
</tr>
<tr>
<td>MRP2</td>
<td>Multidrug resistance-associated protein 2</td>
</tr>
<tr>
<td>MTE</td>
<td>MTE</td>
</tr>
<tr>
<td>OATPs</td>
<td>Organic anion transporting polypeptides</td>
</tr>
<tr>
<td>p53</td>
<td>Tumour protein p53</td>
</tr>
<tr>
<td>P-gp</td>
<td>Permeability glycoprotein</td>
</tr>
<tr>
<td>PICOS</td>
<td>Population, intervention, comparison, outcome and study design</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
</tr>
<tr>
<td>SLC</td>
<td>Solute carrier transporter</td>
</tr>
<tr>
<td>SN-38G</td>
<td>Irinotecan metabolite</td>
</tr>
<tr>
<td>TCM</td>
<td>Traditional Chinese medicine</td>
</tr>
<tr>
<td>Tmax</td>
<td>Time of the peak of maximum drug concentration in plasma</td>
</tr>
<tr>
<td>Vd</td>
<td>Volume of distribution</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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</tbody>
</table>
INTERAKSI HERBA-UBAT DALAM RAWATAN KANSER: ULASAN SECARA SISTEMATIK

ABSTRAK

HERB-DRUG INTERACTIONS IN CANCER TREATMENT: A SYSTEMATIC REVIEW

ABSTRACT

Besides standard anti-cancer drugs, the use of herbs has been steadily increased as complementary and alternative medicine among cancer patients. This may cause potential pharmacokinetic herb-drug interactions at different levels or processes. For this reason, several studies had been conducted to explore any potential changes in pharmacokinetic parameters caused by herb-drug interaction. This review aimed to systematically compile and analyze all the evidence-based findings related to pharmacokinetic herb-drug interaction in cancer treatment which were published from year 2008 to 2019. These articles were searched via electronic databases and selection process was carried out based on the predefined inclusion criterias. The data of the studies were extracted according to bioactive constituents, anti-cancer drug, type of cancer, study design, mode of action and changes of pharmacokinetic parameters. A total of 21 articles reported finding related to pharmacokinetic herb-drug interactions in cancer treatment were included in this review. A total of 10 different herbs and 14 different anti-cancer drugs had been studied for pharmacokinetic interactions. Majority of the articles explained about absorption and metabolism as the main mechanisms which had been induced or inhibited by herb-drug interaction. CYP3A4 was found to be the most targeted anti-cancer drug. The most common method of investigation used in the pharmacokinetic herb-drug interactions was through *in vivo* study. This systematic review also found that breast cancer, docetaxel and ginseng were the most common type of cancer, anti-cancer drug and herb which had been used in investigating the pharmacokinetic herb-
drug interaction respectively. Based on the aforementioned findings, there are still gaps in knowledge regarding pharmacokinetic herb-drug interactions in cancer treatment. Therefore, further research need to be explored and determined in future especially related to its safety and efficacy profiles.
CHAPTER 1
INTRODUCTION

1.1 Background

The Global Cancer Statistics 2018 (GLOBOCAN) reported that about 18.1 million new cancer cases and 9.6 million cancer death occurred in 2018 worldwide. The top 5 causes of cancer death are cancers of lung (18.4%), followed by colorectal (9.2%), stomach (8.2%), liver (8.2%) and breast (6.6%) (Bray et al., 2018). In Malaysia, respiratory malignancy caused 2.3% of total death in 2017 while breast cancer was the most common cause of death among female (4.4%) (Department of Statistics Malaysia, 2018).

Anti-cancer drug or also known as chemotherapeutic drug is one example of method in treating cancer. Each anti-cancer drug exhibit its pharmacological activity based on specific mechanism of cell death. Anti-cancer drugs such as methotrexate, cyclophosphamide, tamoxifen, vincristine and fluorouracil are specific to each type of cancer (Robertson et al., 2016). Examples of chemotherapeutic drugs used to treat lung cancer were albumin bound (nab)-paclitaxel, carboplatin, cisplatin and docetaxel (Gridelli & Sacco, 2016) while tamoxifen is the gold-standard drug used in treating breast cancer (Quirke, 2017). 5-fluorouracil is the most common anti-cancer drug used in colorectal cancer treatment (Cutsem et al., 2014).

Besides standard anti-cancer drugs, the use of herbs has been steadily increased as complementary and alternative medicine among cancer patients. The prevalence of Malaysian herbal users was about 60% among cancer patients, which include vitamin C, evening primrose oil and herbal products (Shaharudin et al., 2011). One of the popular traditional herb, ginseng which contains active compound namely ginsenosides is believed in strengthening body immunity. Besides, it had been showed that ginseng was effective in treating ovary and pancreatic cancers (Sakarkar & Deshmukh, 2011).
Another common dietary herb is ginger which is rich with phenol compound. This compound acts as an anti-oxidant and may help to reduce cancer cell proliferation (Sakarkar & Deshmukh, 2011).

1.2 Problem statement

Despite numerous research focused on combining herbal medicines with chemotherapeutic drugs, limited evidence-based systematic review regarding pharmacokinetic herb-drug interactions in cancer treatment are available.

1.3 Significance of the study

Herbs can influence pharmacokinetic of the administered anti-cancer drugs during absorption, distribution, metabolism and excretion. These modulatory action can be through mechanism-based induction or inhibition of drug metabolising enzymes which subsequently affect the fate of pharmacokinetic of anti-cancer drugs. For this reason, pharmacokinetic herb-drug interaction is one of the important aspect to be studied in affirming their safety and efficacy profiles for the benefits of cancer patient. Therefore, this study aimed to systematically review researches done on pharmacokinetics herb-drug interactions in cancer treatment.

1.4 Objectives of the study

The main objective of the study was to review the pharmacokinetic herb-drug interactions in cancer treatment. Specific objectives of the study were listed as below:

i. to review the in vitro, in vivo and clinical studies of pharmacokinetic interaction between herb and drug in cancer treatment.

ii. to determine number of evidence-based studies related to herb-drug interactions.
iii. to classify herb-drug interactions based on name of herb and its major bioactive phytochemical, name of chemotherapeutic drug and type of cancer.

iv. to classify herb-drug interactions based on changes in pharmacokinetic parameters such as area under concentration (AUC), half-life ($T_{1/2}$), maximum plasma concentration ($C_{\text{max}}$), plasma concentration ($T_{\text{max}}$), clearance (Cl), volume of distribution ($V_d$), absorption rate constant ($K_a$), effective concentration range, toxic concentrations and blood-plasma concentration ratio.

v. to classify herb-drug interactions based on absorption, distribution, metabolism and elimination (ADME) processes.

vi. to review herb-drug interactions in cancer treatment associated with inhibition or induction of P450 enzymes (Phase I Metabolism).
CHAPTER 2  
LITERATURE REVIEW

2.1 Systematic review

Systematic review is defined as a review focused on collection and analysis all evidence based reports that meets inclusion criteria and eligible to provide information for a research question (Liberati et al., 2009). In hierarchy of evidence-based study, systematic review establishes the highest ranking of the quality of the evidence (Burns et al., 2011). Systematic review is consisted of clear-defined research question with transparent methodology, a systematic-structured approach to select studies that fit eligible criteria, involvement of experts in the validation of eligibility of the included studies, and synthesis and presentation of the data analysis of the included studies (Liberati et al., 2009).

The research question of a systematic review has to define the target population, intervention, comparison, outcome, study design, or acronyms known as PICOS (Liberati et al., 2009). Firstly, population should be clearly stated definition of a group of participants such as herbs, and their defining characteristics of interest (eg. active phytochemical compound or herbs extract) and possibly the setting of usage considered, such as usage in cancer treatment. Secondly, the interventions or the exposures need to be reviewed in detail and report systematically. For example, regarding the herb-drug interaction in cancer treatment, reporting various herbs combine use with drug, drug effects after combination with herbs, or the drug efficacy on cancer treatment in different studies. Thirdly, a systematic review needs to mention clearly the comparator (control) group intervention. For intervention of herb-drug interaction study, the drug efficacy without combination of herb may serve as a control for the intervention in cancer treatment. Fourthly, the outcome reports result from the intervention in the study. For example, the enhancement of cytotoxicity in cancer treatment or occurrence adverse
effect after the herb-drug interaction. Lastly, review should record on the the type study design for the included studies, such as *in vitro*, *in vivo*, cohort study or case report (Liberati *et al.*, 2009).

Based on the research question, the series of inclusion and exclusion criterias should be decribed in methods of systematic review. Characteristics of inclusion and exclusion criteria should be practical to extract all studies of interest and not too lengthy that could drag screening time. If the inclusion criterias are too narrowly decribed, there is a possibility of ignorance relevant studies and hardly to set the generalisability of the results. Conversely, if the criteria are too wide, the review may have broad information which is difficult to analyse and synthesis result (Wenden, 2009).

The flow diagram of study selection in a systematic review is illustrated in figure 2.1. Numbers of selected study of all the 4 phases (identification, screening, eligibility and included) should be reported (Liberati *et al.*, 2009). The identification of studies also can be searched through the easily accessible online databases, relevant organizational websites or references lists of papers and journal (Armstrong *et al.*, 2011). After removing duplicated records, screening of titles and abstracts can be done based on the review inclusion criteria. In the eligibility phase, assessment is carried out based on the full-text articles. Further exclusion of the articles is given with valid reason (Liberati *et al.*, 2009). In the final stage of included studies, qualitative and quantitative data synthesis can be generated. Application of spreadsheet workbook may help to record the studies data in categories, such as study population, intervention type, method of study, and outcome of the study. The spreadsheet presentation of data allows the finding for similiarity and differences among of the included studies. Analysis, summarizing and reporting of the findings may give implication and result in answering review question (Armstrong *et al.*, 2011).
Systematic review is based on a structured procedure to gather and combine of various background studies. It is beneficial to researchers and medical practitioners, preventing unnecessary studies and guiding more effective research plan (Armstrong et al., 2011).

2.2 Herbs

The concept of a herbal medicine is defined by the WHO as “Finished, labelled medicinal products that contain as active ingredients aerial or underground parts of plant, or other plant material, or combination thereof, whether in the crude state of as plant preparations. Plant material includes juices, gums, fatty oils, essential oils, and other substances of this nature. Medicines containing plant material combines with
chemically defined active substances, including chemically defined, isolated constituents of plants, are not considered to be herbal medicines (Liu et al., 2015).

Herbs have been widely used for traditional medicine in prevention and treatment since thousands years ago (Che et al., 2013). About 80,000 plant species are employed in health purpose usage in the world (Obodozie, 2012). The examples of most common use of herbs among cancer patients are ginseng and dangqui (Lai et al., 2012). Survey studies of 15 countries which distributed at Asia, Europe and Middle East have shown that the percentage of the usage of herbal medicine is in a range of 9.8%–76% of the overall populations. Japan, South Korea and Malaysia recorded the highest national estimation of complementary medicine use (Harris et al., 2012).

Herbal medicine is defined as whole or part of herbal plant that is used in medical remedies, processed and finished herbal products, and in the form of active phytochemical compounds (Sen & Chakraborty, 2017). The part of plant includes leaves, roots, seeds stems or flowers. Herb can be taken in the form of raw plant or plant extracts, where the plant is dissolved with water, or other solvents like ethanol to separate some of the phytochemicals of this herb. The end-products of the plant extraction contain bioactive constituents, such as alkaloids, flavonoids, glycosides, sterols, and saponins (Nasri, 2016). Currently, polyphenols and terpenoids are two main groups of phytochemical compounds which can be found in many herbal extracts. Polyphenols have great binding ability to glycoprotein whereas terpenoids interfere the permeability of cell membrane (Yang et al., 2014). One herb may contain more than one bioactive compounds. For example, ginkgo has 5 of the flavonol constituents, namely rutin, quercitrin, quercetin, kaempferol, and isorhamnetin. Different concentration of active constituents give variation of biological effect (Bent, 2008).
The active constituents of herbal contribute to anti-cancer function via various mode of action. *Angelica sinensis* contain polysaccharides known as AR-4 which can enhance interferon production to suppress cancer cell growth. It was applied by chinese physicians in cervical cancer treatment (Sakarkar & Deshmukh, 2011). *Allium sativum* contains bioactive contituents such as ajoene, quescetin and cyanidin which possess antioxidant and down-regulating mutagenesis process in cancer development. *Ginkgo biloba* contains Ginkgolide-B that modulates platelet-activity factor to inhibit cancer cell proliferation (Sakarkar & Deshmukh, 2011). More than 70% of chemotherapeutic medicines approved are originated from the plant sources (Sen & Chakraborty, 2017). A proper quality management on herbal medicine is neccessary to maintain the herbal medicine production. Herbal efficacy variation are mainly due to herb factors such as species, active phytochemical compound, extraction procedure and preparation formula (Tarirai et al., 2010).

2.3 Anti-cancer drug

Based on the statistical record of 15 millions Americans with a history of cancer were alive in 2016, number of cancer survivors is estimated increased to 20 millions on year of 2026. The number of cancer survivors continues to increase because of both advances in early detection and cancer treatment (Miller et al., 2016). Cancer treatment includes surgery, radiation therapy and chemotherapy. Chemotherapy employing anti-cancer drugs plays an important role in the metastatic cancer management. Hence, most of the anti-cancer drugs focus on the rapid proliferation process of the cancer cells. Chemotherapeutic drugs can be grouped by following their chemical structure, function and relationship to another drug. The most common categories are alkylating function (e.g., cyclophosphamide, ifosfamide, busulfan), metabolite inhibitors (e.g., 5-fluorouracil, methotrexate, gemcitabine), antitumour agent (e.g., daunorubicin,
doxorubicin, epirubicin), topoisomerase inhibitors (e.g., topotecan, irinotecan, etoposide), and cell cycle suppressors (e.g., paclitaxel, docetaxel, vinblastine) (Sak, 2012).

From 1949 to 2014, US Food and Drug Administration (FDA) recorded and approved about 150 anti-cancer drugs. Anti-cancer drugs can be divided into 2 groups based on drug pharmacological action: cytotoxic based drugs and target-based drugs. The group of target-based drug tended to be increased compared to cytotoxic based drugs. Most targets were either enzyme or receptor which located on the cell membrane (Sun et al., 2017).

Cisplatin is one of the popular chemotherapeutic drug in solid tumour treatment. The multiple mechanisms of killing cancer cells are including generation of reactive oxygen species, stimulation of p53 transduction pathway, alteration cell cycle, inhibition of proto-oncogene mutation and reduction of anti-apoptotic protein production. As a result, cisplatin damages DNA in cancer cells and lead to apoptosis cell death. In order to reduce drug resistance, combination of other drug with cisplatin was applied in the treatment. This practice also helped to reduce cisplatin-induced toxicity to liver, kidney and heart (Dasari and Tchounwou, 2014).

Doxorubicin is one of the anticancer drug that can be used for the cancer treatment such as cervical cancer, endometrium cancer, pancreatic cancer, prostate cancer and breast cancer. Mode of pharmacological action of doxorubicin is targeting on DNA-associated enzymes and altering with DNA base pairs, subsequently resulting in DNA damage which induce cytotoxicity to cancer cells. Besides that, doxorubixin down-regulates anti-apoptotic protein expression. Doxorubicin also stimulates the Bel-2/Bax apoptosis mechanism which downstream cleavage and activation of caspase 9 occurs followed by the cleavage and activation of caspase 3. At the same time,
doxorubicin also induces cell death in other healthy tissues. Unwanted side effect of
doxorubicin is mainly associated with life-threatening carditoxicity (Tacar et al., 2013).

Besides side effects, anti-cancer drug also faces drug resistance problem in
cancer treatment. This can be related to transportation of anti-cancer drug across the cell
membrane, and metabolizing cytochrome enzymes in eliminating anti-cancer drugs.
Most of the chemotherapeutic drugs are substrates for the ATP-binding cassette (ABC)
and solute carrier (SLC) transporters. ABC transporters mediate the efflux of anti-
cancer drugs out of the cells whereas solute SLC transporters are the influx pump to
transport anti-cancer drug into the cells. These influx and efflux pumps influence
intracellular anti-cancer concentration which may influence the efficacy of treatment.
Most of the anti-cancer drug undergoes metabolism of cytochrome enzyme 3A4
(CYP3A4) and again involvement of ABC transporters to remove drug metabolites
compounds out of the cell. As a result, bioavailability of anti-cancer drug become lower
and this lead to the drug resistance (Joyce et al., 2015).

2.4 Herb-drug interaction

Herbs are the most commonly used as a complementary alternative medicine
(CAM) by cancer patients, together with allopathic chemotherapy treatment. Patients
believed herbs can help to regain body immunity, fight against cancer and soothe stress
(Shaharudin et al., 2011). However, a range of 20% to 77% of the patients did not
informed their doctors about their herbs consumption. The main reasons were the
physician’s lack of inquiry; patient’s perception that doctor lack of herb information and
may not encourage the use of herbs; and patient’s thought of the consumption of herbs
was not harm with the conventional cancer treatment (Davis et al., 2012).

Herb-drug interaction can be resulted through modulatory activity on
pharmacokinetics of a drug by the action of herb. Cancer and cardiovascular disease
were the most common referenced disease in HDI studies. There are several interactions which may involve between herb and drug in cancer treatment, and this include pharmacokinetic interactions either through induction or inhibition of drug metabolizing enzymes. For example, induction of these enzyme may often lead to therapeutic failure because of lower plasma levels of the anti-cancer drugs. This may result in unrecognized cancer treatment, which contribute to therapeutic failure (Meijerman et al., 2006).

2.5 Pharmacokinetic interactions

Process of pharmacokinetics herb-drug interactions as well as their potential outcomes are summarized in Figure 2.2. Pharmacokinetic of HDI may cause changes of drug or the herb in the stages of absorption, distribution and excretion. The potential outcome are changes in pharmacokinetic parameters such as $C_{\text{max}}$, $T_{\text{max}}$, $T_{1/2}$, $\text{Cl}$, $V_d$, effective concentration range, toxic concentrations (Tarirai et al., 2010).
Figure 2.2 Summary of HDI based on pharmacokinetic and potential outcome (adapted from Tarirai et al., 2010)

Pharmacokinetic interactions may involve with administrated drug absorption, distribution, metabolism and excretion (ADME) processes. Pharmacokinetic interactions between herb and drug can be measured with several parameters such as area under concentration (AUC), maximum or the highest drug concentration in plasma ($C_{max}$), time needed to achieve the peak of maximum drug concentration in plasma ($T_{max}$), half-life ($T_{1/2}$) and clearance (Cl). AUC is the coverage area under the drug concentration of plasma versus time plotted line curve. Half-life ($T_{1/2}$) indicates time to reduce half of the drug concentration in plasma. Clearance is the measurement of plasma volume which contain certain chemical substance that has been removed outside
of body by excretion such as through urine in a specified time (Urso et al., 2002). Figure 2.3 showed measurement of pharmacokinetic parameter. Information about Cmax, Tmax and T1/2 of a particular drug can be obtained from the graph and these are the examples of pharmacokinetic parameters which normally determined in HDI studies (Tarirai et al., 2010).

![Graph of pharmacokinetic parameters](image)

**Figure 2.3** Measurement of pharmacokinetic parameter.

Absorption of the anti-cancer drugs can be reduced when co-ingestion with herbs that contain gums, hydrocolloidal fibers and mucilage are taken together. These substances tends to mix with drug and reduce absorption on the surface intestine, thus decreasing plasma drug concentration compared to prescription dosage (Obodozie, 2012). Another example is the herbal laxatives such as aloe latex, buckthorn, cascara sagrada, rhubarb, and senna that can cause diarrhea, subsequently reduce intestinal absorption and followed by lower plasma drug concentration, especially drug with narrow therapeutic index (eg, digoxin, warfarin) (Obodozie, 2012).

Distribution of the systemic drug to target organ is depend on drug binding affinity to protein. Herb can interfere drug function by altering the protein-binding. For example, black willow herbs which contain salicylates and can interact with protein-bound warfarin and may cause bleeding. Herb active chemical compounds replace the drug’s protein binding sites result in increased activity of the displaced drug. However,
there are no documented report of displacement of protein-bound drugs for drug distribution in herb-drug pharmacokinetic interaction (Obodozie, 2012).

Metabolism is an important stage of herb-drug pharmacokinetic interaction. Metabolism of drug is multiple biochemical pathway that work together with difference enzymes. The main objective is to biotransform the systemic drug into simpler form and better solubility such that they are easier to be excreted from the body. The liver, gut, lungs and kidney are the organ of metabolism of drug. The main enzymes such as cytochrome P450 (CYP) can be found at the smooth endoplasmic reticulum (Joyce et al., 2015). More than half of all drugs are metabolized by CYP3A4. Herb-drug pharmacokinetic interaction involves alteration of CYP3A4 and other CYPs such as CYP1A2, CYP2C9, CYP2C19, and CYP2D6. Some active compounds of herb mimic to certain drugs and can be substrate of the same CYP isoenzyme. When co-ingestion with such herb, herb with higher affinity to enzyme, may inhibit or induce the activity of the enzyme that could modulate metabolism efficacy of drug (Obodozie, 2012).

Herb-drug pharmacokinetic interaction also can interrupt the clearance of drug through renal excretion. Herbals that can regulate renal tubular reabsorption and secretion of drug should be considered as having potential to produce pharmacokinetic herbal drug interactions (Obodozie, 2012).

2.6 Mechanism of Pharmacokinetic HDI

2.6.1 Efflux transporter

P-glycoprotein (P-gp) is the efflux transporter and is identified as main cause of multi-drug resistance in cancer cells. P-gp is multi-drug resistance protein 1 (MDR1) or also known as ATP-binding cassette (ABC) subfamily B, member 1. P-gp expression
can be found in gastrointestinal, liver and kidney. The function of P-gp is to pump out the intracellular cell substance back into intestinal lumen or plasma via active transportation. Thus, the active P-gp pump can reduce the intracellular anti-cancer drug concentration and cause the drug resistance. Binding between P-gp and its substrate is based on substrate-induced-fit mechanism. Herbal active compounds could regulate P-gp via competitive or non-competitive inhibition or induction. Certain herbal active compound impair P-gp function by altering ATP and suppress the energy source (Tarirai et al., 2010). There was reported auraptene and nobiletin showed enhancement of intracellular daunorubicin accumulation via inhibition P-gp. This study was carried out in vitro in human carcinoma KB-C2 cells (Nabekura et al., 2008). P-gp also drug transporter for other chemotherapeutic drugs such as docetaxel, doxorubicin, etoposide, irinotecan, mitoxantrone, paclitaxel, teniposide, topotecan, vinblastine, vincristine, and tamoxifen (Meijerman et al., 2006).

Another efflux transporter is multidrug resistance-associated protein 2 (MRP2) or ATP-binding cassette (ABC) subfamily C member 2 (ABCC2) which commonly being expressed in any types of human cancer cell lines. As an efflux transporter, MRP2 pumps chemotherapeutic drug out of cancer cell which resulted in reducing its therapeutics effect. The expression of MRP2 also can be found in intestine and other organs. MRP2 primarily binds to hydrophobic anionic conjugates and releases hydrophobic neutral molecules. In the liver, MRP2 delivers hydrophilic compounds such as glucuronide, glutathione and sulfate conjugates into the bile (Tarirai et al., 2010). Inchin-ko-to is a common herbal medicine to treat jaundice in Japan. The study showed that inchin-ko-to could potentiate bilirubin disposal in vivo by enhancing MRP2/MRP2-mediated secretory capacities in both livers and kidneys (Okada et al.,
2.6.2 Influx transporter

Influx transporters control the entrance of substances into the cell. Solute carrier (SLC) transporter proteins such as organic anion transporting polypeptides (OATPs) are the examples influx transporter. OATPs expression is localised in human important organs, such as liver and kidney. Inhibition of OATPs by herbs could lower the intracellular drug and reduce therapeutic efficacy. Conversely, induction of OATPs can cause excess bioavailability of drug and prompt to therapeutic toxicities (Zhou & You, 2007). For example, naringin which is the bioactive compound of grape fruit inhibits OATP 1A2 in vitro decreasing the intracellular of fexofenadine (Bailey et al., 2007). Seville orange also showed inhibition of OATP that decrease influx of drug and lower drug concentrations for both in vitro and in vivo (Farkas & Greenblatt, 2008).
### 2.6.3 Cytochrome CYP 450

Metabolism is the biological process to transform endogenous or exogenous chemical substances into more soluble and simple structure that can be easier to eliminate from the body. There are 2 phases of metabolism of herb and drug. Phase I involves biochemical reactions of oxidation, reduction, hydrolisis and hydration, whereas phase II mostly relates to biochemical reaction of sulfation, methylation, acetylation, glutathione conjugation, fatty acid conjugation and glucuronidation (Tarirai et al., 2010). Cytochrome P450 is the main enzyme family in biotransformation of drug. Drug can be metabolized by such enzyme in liver, intestine, lung and kidney (Joyce et al., 2015).

More than half of the anti-cancer drugs are metabolised by CYP3A4, such as teniposide, etoposide, epipodophyllotoxin, cyclophosphamide, ifosfamide, vindesine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, irinotecan, tamoxifen, tipifarnib, gefitinib and imatinib. Other CYP450 family members such as CYP2A6, CYP2B6, CYP2C8, CYP2C9 are responsible in metabolising both cyclophosphamide and ifosfamide. CYP2D6 metabolises tamoxifen, doxorubicin and vinblastine; while CYP3A5 metabolises etoposide and tipifarnib (Meijerman et al., 2006).

Similar to transmembran transporters, herb is also potential to modulate cytochrome P450 enzymes especially CYP3A4. This action may potentiate herb to interfere with the metabolism of anti-cancer drug. Studies have showed that herb intake during cancer treatment could result in modulating the therapeutic activities of anti-cancer drugs including vincristine, vinblastine, vinorelbine, irinotecan, etoposide, docetaxel, and paclitaxel (Obodozie, 2012).
Herb decreases activity of CYP3A4 through both competitive or non-competitive mechanism. Inhibition of CYP3A4 may cause elevated level of drug bioavailability and probably followed by drug-induced toxicity. Inhibition of CYP3A4 can be characterised by NADPH-, time- and concentration-dependent enzyme inactivation. This may occur after anti-cancer drug is converted into reactive metabolites by CYP3A4 (Zhou et al., 2004). Example of CYP3A4 inhibition caused by HDI was demonstrated in a case report by Bilgi et al., 2010. It was reported that ginseng had interfered the therapeutic action of imatinib in a chronic myelogenous leukemia patient. This patient took Panax ginseng beverage to regain body strength for more than 3 months. Meanwhile, patient was under treatment with imatinib which is substrate of CYP3A4. Ginseng is known as inhibitor of CYP3A4. This resulted in decreasing the imatinib biotransformation, leading to accumulation of intracellular imatinib. As a result, patient induced late-onset hepatotoxicity (Bilgi et al., 2010). Besides that, patient who is undergo cancer treatment with tamoxifen, cyclophosphamide and teniposide is not encourage to take valerian which is inhibitor of CYP2C9 and CYP2C19 (Sparreboom et al., 2004).

On the contrary, herb can also induce the activity of CYP P450 enzymes, for example St John’s wort which had been demonstrated to induce activity of CYP3A4. One study had demonstrated that co-administration of St John’s wort with irinotecan resulted in decreased plasma level of the drug. This may relate to the CYP3A4 induction by St John’s wort which subsequently metabolised irinotecan into reactive metabolite (Hu et al., 2005). Another evidence-based example was demonstrated by an in vitro using hyperforin. Hyperforin is the active biochemical constituent of St John’s wort which had been showed to decrease the intracellular docetaxel in human hepatocytes cultures. Based on this finding, it was suggested that subtherapeutic dosage
of docetaxel may increase after long period consumption of St John’s wort (Komoroski et al., 2005). Besides, echinacea and kava were also reported to induce CYP3A4 activity, which had been postulated not to be consumed to cancer patients who are under treatment with camptothecins (Sparreboom et al., 2004).
CHAPTER 3
Methodology

3.1 Identification

Methods of systematic review as described by Hanan et al., 2018 was applied in the study to identify and screen the articles regarding herb-drug interaction in cancer treatment. There were four stages of systematic review process as shown in Figure 3.1 adapted from Hanan et al., 2018.

![Figure 3.1 Stages of systematic review process](image)

The first stage was identification of journal articles from 5 different electronic databases. Google Scholar, Directory of Open Access Journal (DOAJ), Pub Med, Springer Link and Scopus databases were used to find the related articles based on 3 keywords. Keywords used in this systematic review were herb-drug, interaction and cancer treatment. The last search was performed on 31/01/2019.
3.2 Screening

The second stage of systematic review was employed by screening of all the identified records. The identified journal titles were exported into Microsoft Excel worksheet followed by sorting of the first alphabet in titles to detect and remove duplicate records.

The abstracts of the selected titles were then studied to ensure the suitability of the articles. Selection of articles were based on the inclusion and exclusion criteria as described in (i) and (ii).

i. Inclusion criteria were composed as:
   a. *in vitro, in vivo, or clinical study*
   b. pharmacokinetic parameter, process, mechanism or interaction
   c. chemotherapeutic drug used in cancer treatment only
   d. published between 01/01/2008 to 31/01/2019
   e. only English articles

ii. Exclusion criteria were composed as:
   a. drug for supportive care and medication for comorbid and other illness than cancer (eg. aspirin, warfarin, corticosteroids, phenytoin)
   b. polyherbals
   c. review articles, conference proceedings, survey reports, comments, notes or unpublished data
   d. articles other than English
3.3 Eligibility

In the stage of eligibility, articles were assessed using full-text articles. The articles were then screened by first author for relevance. The selected papers were reviewed by supervisor and co-supervisor, and both had agreed that the papers met the inclusion criteria. Subsequently for the selected eligible studies, the articles were selected based on these exclusion criterias: reason insufficiently described method, evidence of outcome findings is not available or ambiguous.

3.4 Inclusion

The final stage of systematic review was the inclusion of the eligible studies for data analysis. Data were extracted from included articles and classified based on the herb name and its bioactive phytochemical content, name of anticancer drug, type of cancer, experimental condition, mode of herb-drug interaction and changes in pharmacokinetic parameter. Extraction data of the studies was summarized in the table and graph formats.
CHAPTER 4
RESULT AND DISCUSSION

4.1 Number of studies

Total of 720 journal titles were identified from 01/01/2018 to 31/01/2019 by using 5 databases and prescribed keywords. Figure 4.1 showed the number of articles at each stage of data flow diagram of the studies selection results.

![Diagram of data selection process]

After sorting the first alphabet of the identified journal titles in Microsoft Excel worksheet, 65 duplicated journals were detected and discarded. The balance of identified journals was 655.

By using journal abstract, screening was done according to the inclusion criterias as described in Chapter 3 Methodology. Total of 473 articles were excluded because they were not matched inclusion criteria such as review papers, conference
proceedings, survey reports, comments and notes as well as unpublished studies. Examples of the excluded articles were expert opinion of drug interactions between phytotherapeutics in oncology (Haefeli & Carls, 2014), summary and commentaries of Focus on Alternative and Complementary Therapies 2015, survey reports of impact of herb-drug combination among cancer patient (Alsanad et al., 2016), and interview survey for usage of herb (Wu et al., 2011).

The remaining 182 journals were carefully accessed for their eligibility by using their full-text articles. A total of 161 studies were excluded due to an inadequate description on research method or ambiguous findings. For example, study that using polyherbal like Jinfukang contains extracts from 12 botanicals (Cassileth et al., 2013) was excluded. Other polyherbal studies like Shaoyao Gancao Decoction (Yang et al., 2016) and PHY906 (Kummar et al., 2011) were also not eligible. Exclusion also made for the study only reported effects of herb on cancer but not involved with anti-cancer drug interaction, such as studies of cytotoxicity activities of Clinacanthus nutans (Quah et al., 2017) and anti-tumor immune response of Trichosanthin (Cai et al., 2011). Study that involved comorbid illness or supportive care medication, such as midazolam, omeprazole, dextromethorphan and pitavastatin (Seong et al., 2018) was not eligible for included in this study analysis. The remaining articles were carefully analysed, further excluded studies of which not provided complete data. For example study of Astragali radix in breast cancer resistance protein (Lou et al., 2019) and study of Launaea taraxacifolia in Cytochrome P450 inhibition (Thomford et al., 2016) were lack of data on anti-cancer drug effects.

In the final stage of included 21 articles were included in this systematic review. It was notified that a range of 0 to 4 journals were published per year from 01 January 2008 to 31 January 2019 (Figure 4.2).
Data from each study was extracted and tabulated using standardized information, such as scientific name of herb, anti-cancer drug, type of cancer, experimental condition, mode of action, changes in pharmacokinetic parameter, author, journal and year of publication.

4.2 Pharmacokinetic studies

Herb-drug interaction may happen in various form of pharmacokinetic interaction mechanisms or processes. The findings were summarized based on the inclusion criteria and tabulated in Table 4.1.
Table 4.1 Pharmacokinetic (PK) studies of herb drug interaction.

<table>
<thead>
<tr>
<th>Scientific name (Herb name)</th>
<th>Major bioactive phytochemical</th>
<th>Anti-cancer drug</th>
<th>Type of cancer/cancer cell line</th>
<th>Experimental condition</th>
<th>Mode of action</th>
<th>Changes in pharmacokinetic parameter</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Glycine max</em> (Soybean)</td>
<td>30.4% isoflavones as glucosides</td>
<td>Methotrexate</td>
<td>Breast cancer (BCRP-expressing membrane vesicles)</td>
<td><em>in vitro</em></td>
<td>↓ Breast cancer resistance protein (BCRP)</td>
<td>↑Absorption of methotrexate</td>
<td>Tamaki <em>et al.</em>, 2010</td>
</tr>
<tr>
<td><em>Gymnema sylvestre</em> (-)</td>
<td>10.5% gymnemic acid</td>
<td>Methotrexate</td>
<td>Breast cancer (BCRP-expressing membrane vesicles)</td>
<td><em>in vitro</em></td>
<td>↓ BCRP</td>
<td>↑Absorption of methotrexate</td>
<td>Tamaki <em>et al.</em>, 2010</td>
</tr>
<tr>
<td><em>Cimicifuga racemosa</em></td>
<td>Extraction with hydrous ethanol from roots</td>
<td>Methotrexate</td>
<td>Breast cancer (BCRP-expressing membrane vesicles)</td>
<td><em>in vitro</em></td>
<td>↓ BCRP</td>
<td>↑Absorption of methotrexate</td>
<td>Tamaki <em>et al.</em>, 2010</td>
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(↑: Induced or increased, ↓: Inhibited or decreased, -: Not mentioned in the study)
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<tr>
<td>Fructus Schizandrae (-)</td>
<td>Schizandrin A</td>
<td>Doxorubicin</td>
<td>-</td>
<td><em>in vivo</em> (BALB/c nude mice)</td>
<td>↓ P-gp</td>
<td>↑ Intracellular drug accumulation</td>
<td>Huang <em>et al.</em>, 2008</td>
</tr>
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<tbody>
<tr>
<td><em>Convolvulaceae</em> (Morning glory family)</td>
<td>Murucoidin V</td>
<td>Vinblastine</td>
<td>MCF-7/Vin Vinblastine-resistant human breast carcinoma cells</td>
<td><em>in vitro</em></td>
<td>↓ P-gp</td>
<td>↑ Intracellular drug accumulation</td>
<td>Figueroa-Gonzalez <em>et al.</em>, 2012</td>
</tr>
<tr>
<td>- (Citrus fruits)</td>
<td>Auraptene and nobiletin</td>
<td>Daunorubicin</td>
<td>KB-C2 cells multidrug-resistant human carcinoma cells</td>
<td><em>in vitro</em></td>
<td>↓ P-gp</td>
<td>↑ Intracellular drug accumulation</td>
<td>Nabekura <em>et al.</em>, 2008</td>
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</thead>
<tbody>
<tr>
<td><em>Scutellaria baicalensis</em> (Huang Qin or Chinese scullcap)</td>
<td>Wogonin</td>
<td>Docetaxel</td>
<td>Breast cancer</td>
<td><em>in vivo</em> (Sprague-Dawley rat with mammary tumor)</td>
<td>↓ P-gp, ↓ CYP3A</td>
<td>↑AUC, ↑Cmax</td>
<td>Wang <em>et al.</em>, 2018</td>
</tr>
<tr>
<td><em>Piper longum L.</em> and <em>Piper nigrum L.</em> (Long pepper and white or black pepper)</td>
<td>Piperine</td>
<td>Docetaxel</td>
<td>Prostate cancer</td>
<td><em>in vivo</em> (Sprague-Dawley rat)</td>
<td>↓ P-gp, ↓ CYP3A</td>
<td>↑AUC</td>
<td>Li <em>et al.</em>, 2016</td>
</tr>
<tr>
<td><em>Salvia miltiorrhiza</em> (Danshen)</td>
<td>Tanshinones</td>
<td>Docetaxel</td>
<td>-</td>
<td><em>in vivo</em> (Sprague-Dawley rat)</td>
<td>↓ P-gp, ↓ CYP3A</td>
<td>↔AUC</td>
<td>Lee <em>et al.</em>, 2011</td>
</tr>
</tbody>
</table>

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<tbody>
<tr>
<td><em>Panax ginseng</em> <em>C.A. Meyer</em> (Ginseng)</td>
<td>Rd, Rg3, and F2.</td>
<td>Cisplatin</td>
<td>Caco-2 human colorectal cancer cells</td>
<td><em>in vitro</em></td>
<td>↓ Metabolism of intestinal bacteria and mucosa</td>
<td>↓AUC, ↓ Cmax</td>
<td>Zhou <em>et al.</em>, 2019</td>
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<td><em>Panax ginseng</em> <em>C.A. Meyer</em> (Ginseng)</td>
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<td>-</td>
<td><em>in vivo</em> (BALB/c-nude mice)</td>
<td>↓ Metabolism of intestinal bacteria and mucosa</td>
<td>↓AUC, ↓ Cmax</td>
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<tr>
<td><em>Camellia sinensis</em> (Green tea)</td>
<td>Epigallocatechin-3-gallate</td>
<td>Sunitinib</td>
<td>Renal carcinoma cells</td>
<td><em>in vitro</em></td>
<td>↓ Drug solubility under both neutral and acidic conditions</td>
<td>↓ AUC, ↓ Cmax</td>
<td>Ge <em>et al.</em>, 2011</td>
</tr>
<tr>
<td><em>Camellia sinensis</em> (Green tea)</td>
<td>Epigallocatechin-3-gallate</td>
<td>Sunitinib</td>
<td>Gastrointestinal stromal tumor</td>
<td><em>in vivo</em> (Sprague-Dawley rat)</td>
<td>↓ Drug solubility under both neutral and acidic conditions</td>
<td>↓ AUC, ↓ Cmax</td>
<td>Ge <em>et al.</em>, 2011</td>
</tr>
<tr>
<td><em>Salvia miltiorrhiza</em> (Danshen)</td>
<td>Tanshinone IIA and salvianolic acid B</td>
<td>5-fluorouracil</td>
<td>Human gastric cancer cells</td>
<td><em>in vivo</em> (Sprague-Dawley rat)</td>
<td>↑ Drug absorption</td>
<td>↑ AUC</td>
<td>Gu <em>et al.</em>, 2013</td>
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</thead>
<tbody>
<tr>
<td><em>Undaria pinnatifida</em> (Marine brown algae)</td>
<td>Fucoidan</td>
<td>Tamoxifen and letrozole</td>
<td>Breast cancer</td>
<td>Clinical study (cancer patient plasma)</td>
<td>↓ Gastro-intestinal absorption of Fucoidan</td>
<td>↔Trough concentration of tamoxifen and letrozole</td>
<td>Tocaciu et al., 2018</td>
</tr>
<tr>
<td><em>Ginkgo biloba</em> (Ginkgo)</td>
<td>24% flavone glycosides and 6% terpene lactones</td>
<td>Tamoxifen, anastrozole and letrozole</td>
<td>Breast cancer</td>
<td>Clinical study (cancer patient plasma)</td>
<td>↔CYP2C9</td>
<td>↔Trough concentration of tamoxifen, anastrozole and letrozole</td>
<td>Vardy et al., 2013</td>
</tr>
</tbody>
</table>

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Table 4.1 Continued

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</tr>
</thead>
<tbody>
<tr>
<td>Echinacea purpurea (Echinacea)</td>
<td>Alkylamides</td>
<td>Docetaxel</td>
<td>Breast, gastric, oesophagus, bladder, prostate, ovarian, nonsmall cell lung, head and neck cancer</td>
<td>Clinical study (cancer patient plasma)</td>
<td>↑ CYP3A4</td>
<td>↔ Cmax, ↔ AUC, ↔ Half-life</td>
<td>Goey et al., 2013</td>
</tr>
<tr>
<td>Hypericum perforatum (St John's wort)</td>
<td>Hypericin and hyperforin</td>
<td>Docetaxel</td>
<td>Breast, gastric, oesophagus, bladder, prostate, ovarian, nonsmall cell lung, head and neck cancer</td>
<td>Clinical study (cancer patient plasma)</td>
<td>↑ CYP3A4</td>
<td>↓ AUC, ↑ Clearance</td>
<td>Goey et al., 2014</td>
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</tr>
</thead>
<tbody>
<tr>
<td>Angelica gigas (-)</td>
<td>Angelica gigas extract, Hankook Shinyak, Co. (Nonsan, Korea)</td>
<td>Gefitinib</td>
<td>Lung and breast cancer</td>
<td>in vivo (Sprague-Dawley rat)</td>
<td>↓ CYP3A4</td>
<td>↔ Cmax, ↔ AUC, ↔ Half-life</td>
<td>Kim et al., 2018</td>
</tr>
<tr>
<td>Panax quinquefolius L. (American ginseng)</td>
<td>Ginsenosides</td>
<td>5-fluorouracil</td>
<td>Aerodigestive tract, breast, head and neck</td>
<td>in vivo (Sprague-Dawley rat)</td>
<td>↓ CYP2C9 &amp; ↓ CYP3A4</td>
<td>↔ Cmax, ↔ AUC, ↔ Half-life</td>
<td>He et al., 2016</td>
</tr>
<tr>
<td>Trifolium pratense (Red clover)</td>
<td>Isoflavonoids, formononetin, biochanin A, genistein and daidzein</td>
<td>Tamoxifen</td>
<td>Human liver microsomes and HepG2 liver cancer cell lines</td>
<td>in vitro</td>
<td>↓ CYP1a1 ↓ CYP2b2 ↓ CYP3a2 ↑ CYP2c11</td>
<td>↔ Cmax , ↔ AUC</td>
<td>Raju et al., 2015</td>
</tr>
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<td>Isoflavonoids formononetin, biochanin A, genstein and daidzein</td>
<td>Tamoxifen</td>
<td>-</td>
<td><em>in vivo</em> (Sprague-Dawley rat)</td>
<td>↓ CYP1a1 ↓ CYP2b2 ↓ CYP3a2 ↑ CYP2c11</td>
<td>↔ Cmax , ↔ AUC</td>
<td>Raju <em>et al.</em>, 2015</td>
</tr>
<tr>
<td><em>Tripterygium wilfordii Hook F</em> (Leigongteng)</td>
<td>Triptolide</td>
<td>Cyclophosphamide</td>
<td>Non-small cell lung, prostate, or head and neck cancer</td>
<td><em>in vivo</em> (Sprague-Dawley rat)</td>
<td>↓ CYP3A4</td>
<td>↑ Cmax, ↑ AUC, ↑ Half-life</td>
<td>Zhang <em>et al.</em>, 2014</td>
</tr>
<tr>
<td><em>Rhizoma Paridis</em> (-)</td>
<td>Rhizoma Paridis Saponins</td>
<td>Cyclophosphamide</td>
<td>Hepatocarcinoma</td>
<td><em>in vivo</em> (Sprague-Dawley rat)</td>
<td>↓ CYP2B6 ↓ CYP3A4</td>
<td>↑ AUC, ↑ Half-life</td>
<td>Man <em>et al.</em>, 2014</td>
</tr>
</tbody>
</table>

(↑: Induced or increased, ↓: Inhibited or decreased)
<table>
<thead>
<tr>
<th>Scientific name (Herb name)</th>
<th>Major bioactive phytochemical</th>
<th>Anti-cancer drug</th>
<th>Type of cancer/cancer cell line</th>
<th>Experimental condition</th>
<th>Mode of action</th>
<th>Changes in pharmacokinetic parameter</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Marsdenia tenacissima</em> (Roxb.) (Xiao-Ai-Ping injection)</td>
<td>Extraction with chloroform from stems, dissolved in methanol.</td>
<td>Gefitinib</td>
<td>HepG2 cells human liver cancer cells</td>
<td><em>in vitro</em></td>
<td>↓ CYP2D6 ↓ CYP3A4</td>
<td>↓ Intrinsic clearance</td>
<td>Han <em>et al.</em>, 2014</td>
</tr>
<tr>
<td><em>Panax ginseng</em> (Ginseng)</td>
<td>Ginsenosides Rb1 and Re</td>
<td>5-fluorouracil</td>
<td>BGC823 human gastric cancer cells</td>
<td><em>in vivo</em> (Sprague-Dawley rat)</td>
<td>↓ Elimination of the drug</td>
<td>↑ Half-life</td>
<td>Gu <em>et al.</em>, 2013</td>
</tr>
</tbody>
</table>

(↑: Induced or increased, ↓: Inhibited or decreased)
Figure 4.3 categorised the number of articles based on the pharmacokinetic interactions. Based on this pie chart, evidence-based studies conducted on pharmacokinetic herb-drug interactions were involved mainly involved with absorption and metabolism, each comprised of 48%. This was followed by 4% articles related with excretion process. However, none of the article was found related to pharmacokinetic distribution caused by herb-drug interaction in cancer treatment.

![Pharmacokinetic Interactions](image)

Figure 4.3 Percentage of articles in pharmacokinetic interaction.

Based on the ADME process, there were 12 articles described about absorption. This absorption process was reported to change the anti-cancer drug activity through modulation of efflux transporters p-glycoprotein (P-gp) by herb. The active ingredient of *Convolvulaceae* (Morning glory family) is the Murucoidin V, which had been demonstrated to potentially inhibit the P-gp as determined by immunofluorescence flow cytometry (Figueroa-Gonzalez *et al.*, 2012). This result
indicated that Murucoidin V can be a potential efflux pump inhibitor to enhance vinblastine cytotoxicity in preventing multidrug resistance in both drug resistance MCF-7 cells and multidrug-resistant MCF-7/Vin. Another example was demonstrated by Huang and colleagues (2008), whereby five schizandrinins isolated from the *Fructus Schizandrae* were capable to increase accumulation of intracellular doxorubicin. This resulted in reversing the P-gp- mediated multidrug resistance in cancer cells (Huang *et al.*, 2008). In another studies, auraptene and nobiletin had been shown to enhance bioavailability of daunorubicin in human carcinoma KB-C2 cells (Nabekura *et al.*, 2008).

**Scutellaria baicalensis** (Huang Qin or Chinese scullcap) is widely used in traditional Chinese medicine (TCM) for the treating for viral hepatitis, bronchitis, and cancer. Pharmacologically, it exhibits anti-inflammatory, antioxidant and anticancer effects and its main bioactive component is known to be wogonin (Chung *et al.*, 2008). Wogonin had been demonstrated to inhibit P-gp- mediated efflux of docetaxel in rats with mammary tumors (Wang *et al.*, 2018). It was found that co-administration between wogonin and docetaxel had increased C<sub>max</sub> and AUC of docetaxel in rat plasma. These results may also indicate that the presence of wogonin leads to an increase in both therapeutic and toxic effects of docetaxel. *In vivo* study of green tea with irinotecan (Lin *et al.*, 2008), and white or black pepper with docetaxel (Li *et al.*, 2016) may share similarity of action to potentially inhibit P-gp, thus lead to increase AUC and half-life of both anticancer drugs.

Danshen (*Salvia miltiorrhiza*) contains active phytochemical constituent of tanshinones which possesses inhibitory effects on P-gp (Yu *et al.*, 2011) and CYP450 (Chen *et al.*, 2017). On the contrary, co-administration of Danshen did not change pharmacokinetic parameter of docetaxel such as the AUC as observed in both
treated-group and control-group of rats (Lee et al., 2011). Conversely, both active compounds of Tanshinone IIA and salvianolic acid B of Danshen were demonstrated to increase AUC of 5-fluorouracil. The study was done on rat and pharmacokinetic parameter was monitored by high performance liquid chromatography (HPLC). Weight loss was observed in rats most probably related to high absorption of 5-fluorouracil after Danshen treatment (Gu et al., 2013).

The absorption of anti-cancer drug can be also restricted by inhibiting intestinal breast resistance protein. This inhibitory effect on intestinal BRCP can be caused by action of various type of herb including soy bean, Gymnema sylvestre, black cohosh, passion flower and coumestrol (Tamaki et al., 2010). These herbs were demonstrated to increase the absorption of methotrexate by inhibiting BCRP activity in BCRP-expressing membrane vesicles (Tamaki et al., 2010).

*Panax ginseng C.A. Meyer* (ginseng) had been reported to interfere the effect of cisplatin in Caco-2 human epithelial colorectal adenocarcinoma cell line. It was found that co-administration between cisplatin and ginseng had resulted in decreasing the AUC and $C_{\text{max}}$ (Zhou et al., 2019). It was suggested that pharmacokinetic interactions between cisplatin and ginseng may involve with inhibition on metabolism of intestinal bacteria, decrease intestinal absorptive area, and increase efflux ratio of intestinal absorption (Zhou et al., 2019).

*Camellia sinensis* (green tea) is well-known beverage for its anti-oxidant properties. Epigallocatechin-3-gallate (EGCG) is a major constituent of green tea had been demonstrated to interact with sunitinib which resulted in forming sticky semisolid presipitation in mice. This insoluble formation had decreased the intestinal absorption of sunitinib and lower the AUC and $C_{\text{max}}$ of plasma sunitinib. This study
postulated that solubility could be a factor in influencing a drug pharmacokinetics pattern and lowering drug effect in cancer treatment (Ge et al., 2011).

*Undaria pinnatifida* is a marine brown algae which is consumed as dietary supplements due to its reported anticancer effects (Fitton, 2014). This marine brown algae had been characterized to contain fucoidans which is a group of sulfated carbohydrates (Moghadamtousi et al., 2014). However, a study conducted by Tocaciu and colleagues (2018) had demonstrated that co-administration of fucoidan with tamoxifen exhibited no significant changes in trough concentration of the drug as determined by high-performance liquid chromatography charged aerosol detector (HPLC-CAD) using samples from breast cancer patients. Similarly, fucoidan also did not change trough concentration of letrozole in samples from breast cancer patients (Tocaciu et al., 2018).

Trough concentration of a drug is another pharmacokinetic parameter used to determine herb-drug interaction. Vardy and colleagues (2013) had demonstrated that a standardised *Ginkgo biloba* (EGb761) did not affect trough concentration of tamoxifen, anastrozole and letrozole drugs as measured by liquid chromatography tandem mass spectrometry (LC-MS/MS) system using samples from breast cancer patients (Vardy et al., 2013).

Based on pie chart as depicted in figure 4.3, excretion process comprised only 4% of total pharmacokinetic studies which included in this review. For example, Panax ginseng had been showed to significantly increase in the elimination half-life of 5-fluorouracil in Sprague Dawley rat treated group compared to control as measured by HPLC (Gu et al., 2013).

Besides absorption and excretion processes, it was found that nearly half (48%) of ADME-related articles were discussed on the pharmacokinetic metabolism
of anti-cancer drug. Literature searched conceded a total of 12 articles were related to cytochrome P450 (CYP450) enzymes which involved in phase I metabolism. Table 4.2 summarized the mechanism on CYP450 with relevant combination of herbs and anticancer drugs.

Table 4.2 Pharmacokinetic studies based on action on Cytochromes CYP450 (CYPs) metabolism

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Combination (+) of herb and anticancer drug</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition CYP3A</td>
<td>Huang Qin + Docetaxel</td>
<td>(Wang et al., 2018)</td>
</tr>
<tr>
<td></td>
<td>White or black pepper + Docetaxel</td>
<td>(Li et al., 2016)</td>
</tr>
<tr>
<td></td>
<td>Danshen + Docetaxel</td>
<td>(Lee et al., 2011)</td>
</tr>
<tr>
<td>Inhibition CYP3A4</td>
<td>Angelica gigas + Gefitinib</td>
<td>(Kim et al., 2018)</td>
</tr>
<tr>
<td></td>
<td>Tripterygium wilfordii Hook F + Cyclophosphamide</td>
<td>(Zhang et al., 2014)</td>
</tr>
<tr>
<td></td>
<td>American ginseng + 5-fluorouracil</td>
<td>(He et al., 2016)</td>
</tr>
<tr>
<td></td>
<td>Rhizoma Paridis + Cyclophosphamide</td>
<td>(Man et al., 2014)</td>
</tr>
<tr>
<td></td>
<td>Xiao-Ai-Ping injection + Gefitinib</td>
<td>(Han et al., 2014)</td>
</tr>
<tr>
<td>Induction CYP3A4</td>
<td>Echinacea + Docetaxel</td>
<td>(Goey et al., 2013)</td>
</tr>
<tr>
<td></td>
<td>St John’s wort + Docetaxel</td>
<td>(Goey et al., 2014)</td>
</tr>
<tr>
<td>Inhibition CYP3A2</td>
<td>Red clover + Tamoxifen</td>
<td>(Raju et al., 2015)</td>
</tr>
<tr>
<td>Inhibition CYP2B2</td>
<td>Red clover + Tamoxifen</td>
<td>(Raju et al., 2015)</td>
</tr>
<tr>
<td>Inhibition CYP2B6</td>
<td>Rhizoma Paridis + Cyclophosphamide</td>
<td>(Man et al., 2014)</td>
</tr>
<tr>
<td>Inhibition CYP2C9</td>
<td>American ginseng + 5-fluorouracil</td>
<td>(He et al., 2016)</td>
</tr>
<tr>
<td>Induction CYP2C11</td>
<td>Red clover + Tamoxifen</td>
<td>(Raju et al., 2015)</td>
</tr>
<tr>
<td>Inhibition CYP2D6</td>
<td>Xiao-Ai-Ping injection + Gefitinib</td>
<td>(Han et al., 2014)</td>
</tr>
<tr>
<td>Inhibition CYP1A1</td>
<td>Red clover + Tamoxifen</td>
<td>(Raju et al., 2015)</td>
</tr>
</tbody>
</table>

Anticancer drugs are mainly metabolized by CYP450 and biotransformed for degradation and excretion. Herbs can interfere CYP450 function and subsequently influence pharmacokinetic parameters of chemotherapeutic drug.
Hyperforin, one of the component present in St John’s wort extract, had been demonstrated to interfere docetaxel activity through induction of CYP3A4 (Goey et al., 2014). This study demonstrated that metabolism of docetaxel by CYP3A4 subsequently resulted in decreasing AUC and increasing in docetaxel clearance. In contrast, induction of CYP3A4 by Echinacea purpurea did not resulted in significant changes in C_{max}, AUC and half-life docetaxel (Goey et al., 2013).

Besides induction, mechanism-based inhibition of CYP3A4 by herbs had been demonstrated by several studies. For examples, Angelica gigas extract had inhibited CYP3A4, which is known to be the primary enzyme for metabolising gefitinib. This inhibition, however, did not cause significant changes in pharmacokinetics of gefitinib in rats (Kim et al., 2018). CYP2D6 and CYP3A4 are the main enzymes responsible for metabolising tamoxifen. Tamoxifen also can be metabolised by CYP1A2, in which Trifolium pratense (red clover) extract had been shown to inhibit the activity of enzyme in rats. However, this inhibition did not produce significant changes on pharmacokinetics of tamoxifen in rats after treatment with multiple doses of red clover extract (Raju et al., 2015).

Cyclophosphamide exerts its anticancer activity after biotransformation process by CYP450 enzymes. Rhizoma Paridis Saponins herb had been demonstrated to potentially inhibit the activity of these enzymes, namely CYP2B6 and CYP3A4. Inhibitory effects on CYP2B6 and CYP3A4 by this herb had caused significant changes in the AUC and half-life of dapsone and bupropion, respectively (Man et al., 2014). Marsdenia tenacissima extract (MTE) is commonly used as an anti-cancer agent in China. MTE is another example of herb which possesses inhibitory effect on CYP450 activities in liver microsomes. This inhibitory effect had been shown to decrease the in vitro intrinsic clearance (Cl_{int}) of gefitinib (Han et al., 2014).
4.3 Study design of pharmacokinetic studies

Pharmacokinetic herb-drug interactions in cancer treatment had been explored at different types of study design or level, which include *in vitro, in vivo* and clinical study. A total of 21 pharmacokinetic studies were categorised according to the study design, as shown in figure 4.5.

![Study Design of Pharmacokinetic Studies](image)

Figure 4.4 Study design of pharmacokinetic studies.

A total of 13 articles had reported about pharmacokinetic herb-drug interactions in cancer treatment by using animal model (*in vivo*) experimental design. It was the highest study design compared to both *in vitro* and clinical study design. Most of the *in vivo* study had utilised Sprague-Dawley rat (Lin *et al*., 2008; Lee *et al*., 2011; Ge *et al*., 2011; Gu *et al*., 2013; Zhang *et al*., 2014; Man *et al*., 2014; Raju *et al*., 2015; Li *et al*., 2016; He *et al*., 2016; Kim *et al*., 2018 and Wang *et al*., 2018) and 2 studies had used BALB/c nude mice (Huang *et al*., 2008 and Zhou *et al*., 2019) for investigating the pharmacokinetic herb-drug interactions in cancer treatment.

Based on this systematic review, 8 articles were found to be related with herb-drug interactions in cancer treatment at *in vitro* level. Various cancer cell lines
had been used in analysing of pharmacokinetic herb-drug interactions. These include MCF-7 drug resistant human breast cancer cells (Huang et al., 2008 and Figueroa-González et al., 2012), HepG2 human liver cancer cell lines (Han et al., 2014 and Raju et al., 2015), Bel-7402 human hepatic cellular carcinoma cells (Huang et al., 2008), BGC823 human gastric cancer cells (Gu et al., 2013) and Caco-2 human epithelial colorectal adenocarcinoma cells (Zhou et al., 2019).

At clinical investigations, a total of 4 studies had reported the pharmacokinetic herb-drug interactions in cancer treatment. 2 studies were conducted by Goey, et al (2014a, 2014b) using clinical samples from patients whose had suffered with breast, gastric, oesophagus, bladder, prostate, ovarian, nonsmall cell lung, head and neck cancer patients. Several pharmacokinetic parameters were evaluated for determining interactions between Echinacea purpurea and docetaxel or St John’s wort and docetaxel. One clinical study had reported about action of ginkgo in modulating the pharmacokinetic activities of tamoxifen, anastrozole or letrozole among early stage breast cancer women (Vardy et al., 2013). Changes in pharmacokinetic parameters of tamoxifen or letrozole were also evaluated by using clinical samples from breast cancer patients after they had oral intake of fucoidan (Tocaciu et al., 2018).

4.4 Type of cancer studies

In this review, all the included articles were analysed according to the type of cancer. The number of articles was summarized in figure 4.7. Breast cancer was the highest type of the studied cancer which comprised of 9 articles (Huang et al., 2008; Tamaki et al., 2010; Figueroa-González et al., 2012; Goey et al., 2013; Vardy et al.,
2013; Goey et al., 2014; Kim et al., 2018; Tocaciu et al., 2018 and Wang et al., 2018).

![Type of cancer studies Jan 2008-Jan 2019](image)

**Figure 4.5 Type of cancer studies Jan 2008 – Jan 2019**

### 4.5 Type of herb studies

In this review, the included articles were classified according to the herb used in the studies. Table 4.4 listed 10 common types of herbs and their corresponding number of articles.

**Table 4.3 Type of herb studies**

<table>
<thead>
<tr>
<th>Herb</th>
<th>Number of articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginseng</td>
<td>3</td>
</tr>
<tr>
<td>Green tea</td>
<td>2</td>
</tr>
<tr>
<td>Danshen</td>
<td>2</td>
</tr>
<tr>
<td>Soybean</td>
<td>1</td>
</tr>
<tr>
<td>Ginkgo</td>
<td>1</td>
</tr>
<tr>
<td>Echinacea</td>
<td>1</td>
</tr>
<tr>
<td>St John’s wort</td>
<td>1</td>
</tr>
<tr>
<td>Red Clover</td>
<td>1</td>
</tr>
<tr>
<td>Angelica gigas</td>
<td>1</td>
</tr>
<tr>
<td>Fructus Schizandrae</td>
<td>1</td>
</tr>
</tbody>
</table>
Several articles consisted of more than one type of herbs used for investigating pharmacokinetic herb-drug interactions. For example, soybean, *Gymnema sylvestre*, black cohosh, passion flower and coumestrol were used in evaluating the pharmacokinetic parameters of methotrexate (Tamaki *et al.*, 2010). Similarly, Gu *et al.*, 2013 had investigated the mechanism of actions of 2 different herbs, namely ginseng and danshen, on the pharmacokinetic study of 5-fluorouracil.

According to the type of herb, ginseng was the most common herb used in pharmacokinetic herb-drug interactions in cancer treatment (Gu *et al.*, 2013; He *et al.*, 2016 and Zhou *et al.*, 2019). This was followed by green tea (Lin *et al.*, 2008 and Ge *et al.*, 2011) and danshen (Lee *et al.*, 2011 and Gu *et al.*, 2013).

### 4.6 Type of anti-cancer drug studies

According to the type of anti-cancer drug, there were 14 articles described about the pharmacokinetic interactions of these drugs with respective herb in cancer treatment. Table 4.4 listed the number of articles according to the types of anti-cancer drugs.

<table>
<thead>
<tr>
<th>Anti-cancer drug</th>
<th>Number of articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>5</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>3</td>
</tr>
<tr>
<td>5-fluorouracil</td>
<td>2</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>2</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>2</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>1</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>1</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>1</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>1</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>1</td>
</tr>
<tr>
<td>Letrozole</td>
<td>1</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>1</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>1</td>
</tr>
</tbody>
</table>
Similar to the type of herb, several articles consisted of more than one type of anti-cancer drugs used for investigating pharmacokinetic herb-drug interaction (Vardy et al., 2013 and Tocaciu et al., 2018). There were also overlapped of articles which utilising similar type of anti-cancer drug but investigating its pharmacokinetic interaction with different type of herb. Docetaxel was the most frequent chemotherapeutic drug used to investigate pharmacokinetic herb-drug interaction in cancer treatment (Lee et al., 2011; Goey et al., 2013; Goey et al., 2014; Li et al., 2016 and Wang et al., 2018). It was followed by tamoxifen which comprised of 3 articles (Vardy et al., 2013; Raju et al., 2015 and Tocaciu et al., 2018).
CHAPTER 5
CONCLUSION AND RECOMMENDATIONS

5.1 Conclusion

In conclusion, this review had systematically identified, screened and analysed 21 articles related to pharmacokinetic herb-drug interactions in cancer treatment as reported between January 2008- January 2019. Those articles were successfully classified based on the name of herb and its major bioactive phytochemical, name of anti-cancer drug, type of cancer, mode of action and pharmacokinetic parameters. A total of 10 different herbs and 14 different anti-cancer drugs were studied for their herb-drug interactions. Breast cancer was the most frequent type of cancer in pharmacokinetic herb-drug interaction studies. In term of ADME processes, majority of the articles described about absorption (12 articles) and metabolism (12 articles), followed by excretion (1 articles), whilst none article was found for evidence-based findings on distribution. Eleven different combinations between herb and anti-cancer drug had been investigated on their mechanism-based induction or inhibition on CYP450 activities. Pharmacokinetic herb-drug interaction in cancer treatment had been explored at different types of study design or level, which include in vitro (8 studies), in vivo (13 studies) and clinical (4 studies). Based on this figures, there are still gaps in knowledge of pharmacokinetic herb-drug interaction in cancer treatment need to be explored and determined especially for safety and efficacy profiles. Therefore, various level of experimental workflows especially using clinical samples should be investigated in the future. These may also include investigations of herb-drug interaction in cancer treatment at pharmacodynamic, pharmacogenomic and pharmacometabonomic levels. This systematic review may serve as a platform of
information about the pharmacokinetic interactions between herbs and anti-cancer drugs used in cancer treatment.
REFERENCES


