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REVIEW ARTICLE

Real-world Evidence of the Herb-drug Interactions

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Abstract

Herbal medicine (HM) is a type of medicine that uses active ingredients made from plants to treat diseases and maintain health and wellbeing. Due to its increasing worldwide usage, the possibility of HMs and conventional drugs being concurrently used is high, potentially leading to adverse events resulting from herb-drug interactions. Despite the safety concerns regarding such interactions, few studies have been conducted for assessing clinical consequences of using HMs with conventional drugs in real-world settings. As clinical trials are not forthcoming rapidly enough to provide the evidence for herb-drug interactions, observational studies are considered as an alternative approach. The present review focuses on evaluating the utility of analyzing real-world data in observational research to study the clinical consequences of herb-drug interactions between HMs and conventional drugs. The data sources and study designs of each highlighted literature are examined based on its strengths and limitations in analyzing herb-drug interactions. Finally, future observational studies involving novel and rigorous methodologies that may be effective in studying herb-drug interactions are discussed.

Keywords: Herb-drug interactions, Herbal medicines, Observational studies, Real-world evidence

1. Introduction

Herbal medicine (HM) is one of the oldest methods used in treating health-related issues and specializes in the utilization of medicinal plants. Over the years, HM has been increasingly used by countries worldwide for various health benefits and disease treatments. The World Health Organization has stated that an estimated 80% of the world's population is using herbal products for health care reasons, particularly in developing countries where HM is often considered as a primary source of healthcare treatment [1]. In India and Africa, 70–90% of the country's population takes HMs, respectively, while 40% of the healthcare in China involves HMs [2]. With the rapid growth of HMs usage, the concerns about the potential herb-drug interactions remain when HMs are concomitantly used with conventional drugs (i.e., standard medicines prescribed in the medical system). A systematic review has recently reported a substantial concurrent use of HMs and conventional drugs among older adults [3]. In addition, there is a tremendous increase in the use of HMs over the last few decades, estimating that around 20–35% of patients prescribed on conventional drugs are also taking herbal products [4]. Given these findings, it is very likely that HMs are concurrently used with conventional drugs among patients seeking treatments in general. Yet, despite its increasing popularity, many public health issues and safety concerns of concomitant use of HMs and conventional drugs are currently left unanswered.

To date, few studies have been conducted to examine the prevalence of co-utilizing HMs and conventional drugs, and even fewer studies were performed to evaluate the safety and effectiveness of herb-drug interactions. Typically, a randomized controlled trial (RCT) is the gold standard method used to determine the efficacy of drugs; however, in the case of HM, ethical considerations, fragmented health care system, and the highly individualized dosing regimen of herbs make the situation difficult for researchers to conduct RCTs when investigating

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the clinical consequences of herb-drug interactions [5]. In addition, HMs can be used at different dosages depending on the symptoms of disease, making it difficult for RCTs to comprehensively reflect HMs usage in real-world settings [6]. Furthermore, as RCTs are usually conducted in a controlled setting with selected patients, certain proportion of patients in a population may be under-represented, thus affecting its generalizability due to their rigorous inclusion and exclusion criteria. As clinical trials are not advancing fast enough to meet the public's need for knowledge on the effectiveness and safety of herb-drug interaction, alternative research methods should be considered.

Currently, the main alternative approach to conducting herb-drug related studies involves the utilization of observational studies to gather real-world evidence, which comprises the information generated from real-world data via multiple possible sources such as administrative claims database, hospital records, and surveys [7]. Despite certain limitations, real-world studies allow researchers to examine the effects of herb-drug combinations outside of controlled settings, even at a population level [7]. Accordingly, real-world evidence from observational studies is essential in bridging this gap to provide the swift information on the utilization, effectiveness, and safety of HMs and to study the clinical consequences from any interactions with conventional drugs. Owing to the lack of a comprehensive review concentrating on real-world evidence of beneficial or harmful effects from the combined use of HMs and conventional drugs in prior literature, this review article aimed to evaluate the utility of analyzing real-world data in observational research studying the clinical consequences of concomitant use of HMs and conventional drugs, primarily through the elucidation of the adopted data sources and study designs and the discussion on future research directions.

2. Real-world data sources

At present, observational studies have been performed to utilize real-world data for assessing potential herb-drug interactions. In this review paper, we discussed the strengths and limitations of utilizing real-world data via observational methodologies to study the potential herb-drug interactions between HMs and conventional drugs. In addition, we evaluated whether real-world evidence generated by observational studies is a useful tool in studying this field of interest by discussing the currently adopted methods and the state-of-the-art pharmacoepidemiologic approaches that can be utilized in the future.

2.1. Health insurance claims database

The first approach to conducting real-world study on the herb-drug interactions is the one that uses health insurance claims database as the data source. Health insurance claims database is a largescale electronic record that provides demographic information and clinical data and is often used in observational studies to obtain real-world evidence. For instance, the Taiwanese National Health Insurance Research Database (NHIRD) is one of the largest health insurance claims database around the world and it covers comprehensive information on encrypted demographics (date of birth and age), disease diagnoses, procedures and prescribed medications (including conventional drugs and Chinese HMs) from outpatient, inpatient and emergency care. In the NHIRD, detailed drug records contain drug names, prescription dates, prescription refill dates, total doses, days of supply, and frequency of drug usage [8]. Despite abundant drug information contained in health insurance claims databases, these data cannot directly reveal whether there are any clinical consequences from exposure to herb-drug interactions because there is no column in the database to indicate this kind of information. Therefore, to assess whether exposure to herb-drug interactions could cause a beneficial or harmful effect in the real-world, a health insurance claims database needs to be assessed, analyzed, and coupled with an appropriate observational study design and statistical approach.

Although health insurance claims database is commonly used as a data source for clinical researches [8], there are only a few studies that have utilized this approach to examine the clinical consequences of herb-drug interactions. To date, the majority of studies that used health insurance claims database focused on the effects and safety of HM alone while only a handful of studies explored potential herb-drug interactions (i.e., without examining the hard end points associated with the aforementioned interactions) among patients with various diseases.

Of the very few studies that utilized health insurance claims database to examine the clinical consequences associated with the exposure to the combined use of HMs and conventional drugs, the cohort study by Hsu et al. analyzed a nationwide health claims database and revealed a decreased risk of endometrial cancer associated with the use of Chinese herbal product *Ginseng* among breast

cancer (BC) survivors treated with tamoxifen [9]. The study became the first of its kind to report such an association and found the possible beneficial interactive effects between *Ginseng* and tamoxifen in regard to endometrial cancer development among BC survivors. Another cohort study by Wu et al. also found the inhibition of the subsequent endometrial cancer among the same tamoxifen-treated BC population concomitantly receiving the herb *Dang-qui* [10]. This study suggested that the association observed may be due to a mechanism that involves the inhibition of MGMT protein expression, resulting in a synergistic antiproliferative effect upon the combined use of *Dang-qui* and tamoxifen use. While further research is definitely needed to confirm the findings from the study by Hsu et al. and Wu et al., both studies serve as the stepping-stones in understanding the effectiveness of using tamoxifen with *Ginseng* and *Dang-qui*, respectively. Their findings also pointed out that the clinical consequences from herb-drug interactions could be beneficial. On the other hand, a cross-sectional study with analysis of the Taiwan National Health Insurance Research Database (NHIRD) reported no increased risk of hemorrhage with the concurrent use of the herbal medicine *Gingko biloba extract* (*GBE*) and antiplatelet/anticoagulant agents, but found the univariate estimate of relative risk for hemorrhage in older patients ($\geq$65 years old) to be significant [11].

Based on the three studies discussed, there are several strengths that are worth mentioning with regards to using health insurance claims database as the data source for conducting herb-drug related researches. All the studies were able to obtain the information from a nationwide health insurance claims database, allowing not only a relatively large sample size but also increasing the overall generalizability of the findings due to its nationwide scale. In addition, due to the nature of using claims database, minimum recall bias and higher congruence with patients' medical records compared to that with data obtained from questionnaires may be expected. The three studies also all happen to be conducted in Taiwan, even though these studies were not intentionally selected, suggesting that the possibility of using health insurance claims database to study potential herb-drug interactions is currently a challenge in other countries due to the lack of coverage of HM in their respective health insurance programs. In Taiwan, on the other hand, the coexistence of conventional drugs and HMs, particularly Chinese herbs, is a notable feature in the health care system, an aspect that may have stemmed from its long history in developing and utilizing HMs. The NHIRD utilized by the three studies provides not only prescription-refill data and dosage records of conventional drugs but also the information on HM formulae and single herbs, allowing population-based studies to be performed.

Using health insurance claims database, however, also comes with certain limitations [8]. As acknowledged by all the studies, the database does not include over-the-counter prescriptions of conventional drugs or HMs, nor does it factor in the possibility of herbs being consumed in health foods. As a result, the co-prescription of HM and conventional drug may be underestimated. In addition, all three studies had incomplete comparability in terms of the baseline characteristics between comparison groups, in which only the bare minimum characteristics were presented. It is also unclear whether baseline characteristics were balanced during subgroup analyses. Furthermore, there seems to be no statistical adjustments made for imbalanced comorbidities and co-medications in each respective study, raising the concern for potential confounding. Lastly, even though the Taiwanese national health insurance claims database includes records of HMs, it is still limited to herbal products that are reimbursed in the health care system, meaning that certain HMs may still be unavailable for being evaluated as real-world data. Thus, the approach of using claims database to study potential herb-drug interactions may be currently limited to certain HMs and countries only.

2.2. Electronic health records

The second approach to studying herb-drug interaction in real-world settings involves utilizing electronic health records (EHR) as the data source. EHR is a longitudinal collection of electronic records of a patient's medical information as well as administrative encounters between the patient and their health-care provider [12]. It is essentially an electronic copy of a patient's medical chart that includes their past medical history, treatment plans, diagnoses, and laboratory results. While the EHR system is considered as a common and useful tool in the health-care settings, it is not commonly used as the sole data source in herb-drug related studies.

Among the few studies that only utilized EHR as their data source, the prospective cohort study by Lopatin et al. was conducted at 16 clinical centers to evaluate the following three treatment options for chronic rhinosinusitis (CRS): oral antibiotics plus the herb *Cyclamen europaeum* (*CE*), *CE* in monotherapy, and oral antibiotics alone [13]. By analyzing multicenter EHRs, this study was able to show that

CE in monotherapy or in combination with a standard oral antibiotic significantly reduced CRS symptoms and recurrences compared to oral antibiotics alone among patients with CRS exacerbation. Thronicke et al. also conducted an observational cohort study using EHR to analyze the rate of adverse events (AE) among cancer patients who took immune checkpoint inhibitors (ICM) with and without the herbal medicine *Viscum album* L. (*VA*); however, no significant differences in the AE rates were found between the two groups [14]. Despite the comparable results of AE rates across both groups, this study was the first to give an insight on the application of herbal medicine *VA* in patients with metastatic or advanced cancer and it provided a first impression on the safety aspects of using *VA* and ICM concomitantly.

The strengths of utilizing EHR as the data source are similar to those of claims database. However, one main difference between the two data sources is the additional laboratory records that EHR provides. As EHR can obtain large datasets that include extensive laboratory data and hospital test results, it provides an additional layer of information about the patients that could potentially be impactful to the study outcome. Loptain et al. demonstrated this by incorporating the nasal endoscopy test to objectively assess the study outcome in their herbal-drug research, thus reducing the possibility of outcome misclassification [13]. Coupled with the fact that EHR can also provide records on HMs that are not exclusively limited to reimbursed herbs, this data source provides a relatively complete dataset for analysis.

Based on the studies mentioned, EHRs also possess several limitations. The most notable one reported in the studies is the potential confounding by indication bias: as both studies determined the allocation of patients to treatment groups at the discretion of the physicians, it is likely that physicians may reserve the combined treatment of herbal and conventional drug for patients who have symptoms with greater severity. Additionally, the possibility of patients seeking treatment in other health-care facilities cannot be ruled out, which may be a potential issue as not all electronic records are linked. This is due to the fact that there are multiple EHR systems across hospitals, sometimes even hundreds depending on the country, across a population, each with their own customizations and interfaces that make it difficult for medical records to be integrated. Furthermore, while EHR can indeed provide data on non-reimbursed HM, this data source still cannot encompass all the herbs that a patient may have taken.

2.3. Questionnaire

Another approach that is commonly used in real-world studies for evaluating potential herb-drug interactions is the utilization of questionnaires. Questionnaire is a type of research tool that can be used to collect a variety of information from the respondents depending on how it is designed. When designing a questionnaire, questions raised need to be reliable and valid [15]. The reliability and validity of a survey refer to consistent measures across different questions in a domain and high degree of respondents' answers to questions mapping on to what a study intends to measure, respectively [15]. Accordingly, multiple scenarios need to be avoided when designing questionnaires, such as inadequate wording, poorly defined terms, and confusing questions as well as leading the patients to answer in a specific way [15]. Given its relatively flexible and cost-efficient nature, questionnaire is one of the most frequently used approaches adopted in the studies assessing potential herb-drug interactions. The aforementioned reviewed studies utilizing questionnaires all assess potential herb-drug interactions rather than the actual interactions probably because outcomes are difficult to be determined from surveys. Additionally, observational studies using questionnaires determined potential herb-drug interactions with references to multiple sources of information, such as databases, websites, and literature with documented or theoretical potential interactions between HMs and conventional drugs.

Among many studies that used questionnaires as the data source for their research, Jermini et al. conducted a cross-sectional study on the concurrent use of cancer treatment with complementary and alternative medicine (CAM), a wide range of medical treatments that include the use of HM, to evaluate any potential interactions [16]. While the study reported the prevalence of CAM use to be 45% in patients receiving cancer treatments, no associations were found to be clinically concerning in terms of pharmacokinetic interaction potential. The researchers attributed this lack of association to the fact that the questionnaire was conducted in only a single hospital, resulting in the low rate of HM use in their sample size. Contrastingly, Loquai et al. conducted their cross-sectional study in 7 skin-cancer centers and reported potential herb-drug interactions in 23.9% of patients concomitantly receiving cancer treatment and CAM [17]. This study was the first in its field that utilized the questionnaire-based approach to study potential interactions between CAM and antineoplastic

treatment among melanoma-diagnosed patients. Moreover, Djuv et al. conducted an herb-drug interaction study from a different angle by focusing on patients who had consultations with general practitioners [18]. By utilizing the questionnaire methodology, the study reported 255 herb-drug combinations among the study population, 18 of which were found to be at risk of clinically relevant interactions, including antihypertensive and diuretic drugs with *Ginseng*. As only a handful of research has examined the concurrent use of HMs and conventional drugs in primary care settings, this is one of the few studies that evaluated patients in general practice on the co-use of herb-drug combinations and their potential interactions. McLay et al., on the other hand, performed a cross-sectional survey on pregnant women and found that 12.7% of the study population was exposed to herb-drug interactions with the potential to increase the risk of various adverse events, including postpartum hemorrhage, maternal and fetal central nervous system depression, and alteration of maternal hemodynamics [19].

Considering all the studies mentioned, a number of strengths merit the discussion pertaining to the use of questionnaires as a data collection tool for herb-drug related research. Due to the nature of this observational method, questionnaires usually require less time compared to other data sources and are relatively cost-efficient to perform. As researchers can decide the structure and format of the questionnaire, this approach provides not only data collection on HM and conventional drug use, but also the information on any lifestyle drugs that may not have been captured in the health insurance claims database or EHR. An example of this is the study by McLay et al., in which 40% of pregnant women in the UK were reported to self-administer HMs and natural products as additional nutrients for their fetuses despite being on prescribed drugs [19]. In addition, questionnaires also give further insights on the current situation of herb-drug use in health care settings; Djuv et al. demonstrated this in their study, reporting that 80% of patients who co-used HMs and conventional drugs did not inform their physicians and doctors about their herbal use [18]. With the majority of the respondents stating that they simply were not asked about HM consumption, this implies a strong indication for health care professionals to take the initiative to inquire and identify potential herb-drug interactions.

Despite the flexibility and wide coverage of information that questionnaires can provide, this data source also has several limitations. One of the biggest factors that can affect the data collected from questionnaires is how the questions are designed. Depending on whether the questions are close-ended, open-ended, or a mixture of both, bias and skewed feedbacks may occur. Based on the studies discussed, Djuv et al. and McLay et al. both provided a list of herbal products, 24 and 40, respectively, in their questionnaire that they considered to be commonly used. This may be a concern as it can restrict the patients' answers and lead them into certain directions depending on the content of the list [18,19]. Additionally, none of the mentioned studies were able to validate the data they obtained from the questionnaires since no EHR or health insurance claims database were utilized. Furthermore, there is currently not a designated database or "gold standard" database that serves as the main source for providing comprehensive information on the references to potential herb-drug interactions. In other words, studies conducted via questionnaires have to rely on various sources of information to evaluate the potential interactions they have identified. This cross referencing among multiple databases to determine clinically relevant herb-drug interactions may lead to heterogeneity across different studies. Accordingly, although employment of questionnaires may be a convenient and accessible tool to study potential herb-drug interactions, such method is still limited in its generalizability and function due to the nature of its design.

2.4. Survey and electronic health records

The last commonly used approach to examining herb-drug interactions is one that combines the observational methodology of survey and EHR together. While utilizing questionnaire alone is effective in collecting multiple insights simultaneously, including information on potential herb-drug interactions and confounding variables, it is still limited by its lack of validity. As such, many studies have combined the utilization of survey and questionnaire with EHR as a hybrid approach in studying the interactions between HMs and conventional drugs. In this hybrid approach, both survey and EHR would be used as data sources to collect information on herb-drug use from the population of interest, providing a further examination on the current medicines consumed by patients.

Of the numerous studies that used survey and EHR to investigate herb-drug interactions [20–23], Chi et al. found that among the elders aged 60 and above, 43.3% of the participants who had concurrent use of HMs and conventional drugs were exposed to

potential herb-drug interactions, with half of the interactions related to HM with anticoagulant properties [24]. Chi et al. analyzed the EHR to measure important relevant data, including demographic characteristics and physician-diagnosed history of chronic diseases, and adopted the survey method to identify all medication use, including HM, to which they later confirmed in medical records. By utilizing both observational methodologies, this cross-sectional study was able to find the most common HMs and conventional drugs involved in the identified interactions, including herbs of *Ginkgo* and *Ginseng*, and conventional drugs of antithrombotic agents and calcium channel blockers. Their data provided the awareness and emphasis on the common herb-drug combinations. Levy et al. also conducted a cross-sectional study using the survey and EHR hybrid approach and found that 16.5% of the herb-drug users hospitalized in surgical departments had severe or moderate potential interactions with anesthetic drugs [25]. Furthermore, 19% of the herb-drug users also had the potential to develop perioperative hemorrhage due to herbal interactions with antithrombotic drugs. Even with its limited sample size, this study is one of the few studies that systematically analyzed the potential herb-drug interactions in a perioperative setting. On the other hand, Drozdoff et al. utilized the survey and EHR hybrid approach and observed high overall use of HMs and conventional drugs among patients undergoing chemotherapy for breast and gynecological cancer, reporting 18.1% of herb-drug users to have potential interactions between HMs and metabolized anticancer drugs, despite very few of the interactions considered to be clinically relevant [26]. Al-Ramahi et al. also reported few potential herb-drug interactions to be clinically relevant with employment of the combined survey and HER approach [27]. While the two abovementioned studies did not find many clinically relevant interactions, their findings may still be used as a starting point in that specific field of interest. Additionally, another two studies using surveys with EHRs assessed the safety of herb-drug interactions. Levy et al. found that approximately half of the patients took HMs during hospitalizations. Of them, 47% had at least one potential herb-drug interaction, which might influence drug metabolism and cause serious adverse effects, such as bleeding or hypotension [28]. Another study conducted by Leung et al. reported a high prevalence of HMs use in patients receiving warfarin, but revealed no association between the exposure to HMs and an increased risk of self-reported bleeding events. It is worth noticing that even though the standardized and fixed questions used in the structure survey used in Leung et al.'s study might increase reliability, it could avoid participants to respond in much detail. In addition, the duration of HM usage was vaguely defined [29]. To sum up, although the combined use of survey and EHR allows more comprehensive information on herb-drug use, it should be cautious about the potential methodology flaws, such as limited sample size and recall bias. Future studies with bigger diverse populations and further utilization of EHR in this hybrid approach is needed, such as assessing hard-end outcomes from EHR. Overall, current literature adopting the survey and EHR combination approach primarily employs questionnaires to obtain the information on the combined use of HMs and conventional drugs and accesses EHR to validate patients' reported data or to obtain clinical hard-end outcomes.

The strengths of conducting studies via the survey and EHR approach are similar to those that utilize the two data sources alone. As mentioned previously, surveys have the advantages of collecting the information on multiple herb-drug combinations at once while EHR can provide higher accuracy of medication usage than surveys. Based on the studies discussed, the addition of utilizing EHR on top of surveys allows researchers not only to confirm the use of HMs and conventional drugs that were disclosed in the surveys but also to examine patients' medical history that may be used to assess hard-end outcomes and confounders. As EHR provides records that are physician-diagnosed rather than self-reported, the accuracy of the information on herb-drug use is moved up to another level compared to the studies that utilize either surveys or questionnaires alone. Additionally, this hybrid approach of survey and EHR has the potential to look at actual interactions between HMs and conventional drugs rather than just theoretical assessment; however, few studies have attempted this thus far, suggesting a possible direction for future studies.

Conducting real-world studies via survey and EHR also possesses certain limitations. While EHR does provide an extra level of accuracy in data collection, not all HMs are always confirmed or collected in medical records as they can be taken as self-medication, or patients are simply not asked about history of herbal usage. Therefore, the potential herb-drug interactions detected in observational studies that utilize this hybrid approach may still be underestimated. In addition, although EHR can provide data on comorbidities and comedications of patients, previous studies did not seem to fully utilize this data source to adjust for patients' comorbidities and comedications while assessing

herb-drug combinations. Instead, the majority of studies that used survey and EHR for real-world data mainly focused on the prevalence of theoretical and potential interactions between HMs and conventional drugs. Furthermore, similar to the studies that solely used either surveys or questionnaires as their only data source, research that implemented the hybrid approach still requires the use of various sources of online database (i.e., cross referencing) to evaluate potential herb-drug interactions. This remains an issue as utilizing multiple databases for referencing potential herb-drug interactions creates inconsistency that may cause different studies to reach different conclusions about the same herb-drug combination. Despite these limitations, the concurrent use of survey and EHR is arguably one of the most common approaches observed in studies regarding herb-drug interactions, possibly due to its richness of available data compared to other data sources, such as health insurance claims database. A summary illustrating the differences in the strengths and limitations of each data source can be found in Table 1.

3. Study designs

Four common data sources were previously discussed in regard to their strengths and limitations when used as real-world data to study the interactions between HMs and conventional drugs. However, among the examined studies, only two types of study designs were implemented: the more frequently used cross-sectional design and the less commonly adopted cohort design. Similar to the data sources, different study designs also possess their own advantages and shortcomings that may affect the findings of the research (Table 2). The following aimed to explore and discuss the main strengths and drawbacks of these study designs to obtain the real-world evidence of the interactions between HMs and conventional drugs.

In terms of the most frequently used study designs in the aforementioned and discussed literatures, a cross-sectional study design is the most dominant approach observed in the hybrid and questionnaire only studies. Its frequent usage in this field of interest may be attributed to certain strengths. First, a cross-sectional design is often regarded as a relatively quick and easy method to perform than most of the study designs as it requires little or even no waiting time for the outcome to occur [30]. As a result, it provides rapid results of descriptive information such as the prevalence of herb-drug interactions and their distribution patterns in real-world settings. In addition, a cross-

Table 1. Summary of strengths and limitations of the common data sources used in observational studies.

Data Source	Strengths	Limitations
Health Insurance Claims Database	- Good generalizability - Minimum recall bias - Provides herbal medicine formulae and records (country-based) - Provide data on comorbidities and co-medications of patients	- Exclusion of over-the-counter records, possible underestimation - Limited to records of herbal medicines that are reimbursed - No laboratory data available
Electronic Health Records (EHR)	- Laboratory data available - Herbal medicine records not limited to reimbursed ones - Provide data on comorbidities and co-medications of patients	- Exclusion of over-the-counter records, possible underestimation - EHRs not always integrated among different hospitals
Questionnaire	- Relatively quick and cost-efficient - Provides information aside from medical records (lifestyle) - Collect data on multiple exposure combinations at once	- Issues of reliability and validity of items generated in questionnaires - Lack of validation for answers obtained from questionnaire - Requires online database to evaluate potential herb-drug interactions, possible heterogeneity
Survey and EHR	- Able to confirm medical records reported from surveys via EHR - Higher accuracy of data due to physician diagnosed records - Potential to assess hard-end outcomes with EHR	- Possible underestimation of potential herb-drug interactions - Requires online database to evaluate potential herb-drug interactions, possible heterogeneity

Table 2. Summary of strengths and limitations of the common study designs used in the observational studies for evaluating herb-drug interactions.

Study Design	Strengths	Limitations
Cross-sectional	- Relatively quick and easy to perform, provides rapid descriptive results - Allows assessment of multiple interactions simultaneously - Give insights on prevalence of herb-drug interactions - Can generate hypothesis for future studies	- Cannot establish causal relationships due to temporality of association - Not ideal for studying rare outcomes or rare exposure - Prone to survivor bias
Cohort	- Clarity of temporal sequence, can establish causal relationships - Allows calculation of incidence rate of outcomes - Can assess multiple effects of a single exposure	- Not appropriate for assessing rare outcomes - Differential losses to follow-up can result in bias - May have limited/incomplete data in retrospective studies - Can be time-consuming in prospective studies - Issue of long latency period - Prone to confounding by indication bias and immortal time bias
Case-control	- Can assess multiple exposures - Appropriate for rare outcomes - Appropriate for latent outcomes	- Prone to selection bias - Unable to observe incident outcomes - Weak temporal relationship
Case reports/case series	- Easy to perform - Likely to report a new association of interest for the first time - Provide information for generating hypotheses	- Lack of control groups - Cannot establish a causal relationship - Limited generalizability

Note. Only cross-sectional and cohort studies were employed for the reviewed studies utilizing real-world data.

sectional study design allows researchers to assess the associations of multiple interactions simultaneously and to generate research hypothesis that may be tested for future in-depth studies [30]. As studies regarding actual interactions between HMs and conventional drugs are currently still limited, research carried out using this study design may shed light on herb-drug interactions that are especially common and important to look further into.

Cross-sectional designs, however, also retain some limitations. As cross-sectional studies measure both exposure and outcome either at a single point in time or over a short time period, the temporality of the association between exposure and outcome occurrence is uncertain [31]. Accordingly, while it is possible to evaluate associations of herb-drug combinations with potential confounders, studies using this design method cannot determine whether the exposure of HMs with conventional drugs precedes the outcome of interest, making it difficult to prove causality. Additionally, cross-sectional studies are not ideal for studying rare outcomes due to the difficulty of observing a sufficient number of outcome events and the potential of survival bias [31]. Nevertheless, cross-sectional studies are still useful in the sense that they can provide valuable descriptive feedbacks to inform health care services on the planning of their resources and serve as the first step of a research topic or a pilot study for future prospective studies.

Cohort study design, on the other hand, is only adopted in studies that utilized either the health insurance claims database or EHR as a data source, albeit very few. Despite its less frequent usage in assessing herb-drug interactions, cohort design has several strengths that are worth mentioning. Perhaps one of the biggest advantages in adopting a cohort study design is its clarity of temporal sequence [32]. In other words, it allows researchers to calculate the incidence rate of the outcome of interest as the exposed and unexposed groups are identified and subjects with the outcome of interest are excluded at the beginning. Both groups are then followed over time for various outcomes, which establishes the time sequence of events. Cohort design could be especially useful when trying to demonstrate an association between the exposure to the combined use of HMs and conventional drugs and the risk of subsequent clinical consequences since the temporality between the exposure and outcome is well defined [32]. Furthermore, cohort studies have the ability to study multiple effects of a single exposure, allowing studies to look at several adverse and/or beneficial effects of a specific herb-drug combination at once [33].

The limitations of utilizing a cohort study design also warrant some discussion. While cohort studies have the advantage of examining the temporal relationship between an exposure and an outcome, the differential losses of follow-up can introduce bias to the study [31]. The existing data used in retrospective cohort studies is also limited in its quality and completeness because exposure and outcome data as well as patients' characteristics may have already been recorded. This can result in an underestimation of the herb-drug combination of interest or lead to the misclassification in the measurement of combined use of HMs and convention drugs or clinical events of interest. For studying rare outcomes, in order to allow enough outcomes to occur, prospective cohort studies can be very time-consuming because the study subjects are required to be followed for a long period of time, and retrospective cohort studies need to be conducted via a data source with long-term data, making a cohort study design inefficient in assessing this type of outcome [30]. Moreover, when conducting a cohort study, there is also the possibility and concern of long latency period for certain herb-drug interactions, making it difficult for researchers to delineate a causal relationship between exposure to herb-drug interactions and the outcome of interest. Lastly, cohort studies in general are prone to confounding by indication bias and immortal time bias, which should be addressed in the early phase of designing cohort studies [34].

4. Comparisons of the findings from current review with prior literature

Previous literature that reviewed clinical data of herb-drug interactions was dominated by case reports [35,36], which were distinctly different from the examined observational studies in this review. Izzo conducted an overview of herb-drug interaction reports and observed that the majority of the assessed interactions had a negligible clinical significance, while concomitant use of St. John's wort with certain types of antiretroviral, anticancer, immunosuppressive agents may cause serious adverse events [35]. Notably, the overwhelming majority of the data provided by Izzo were case reports; therefore, it is difficult to infer a causal relationship from these case studies. Another review on this herb-drug interaction topic documented 15 cases of adverse drug reactions among the examined 51 studies, among which 49 were case reports [36]. The dominant case reports in the review by Awortwe et al. [36] also limited the utility of the provided information due to the nature of case-report studies. Taken together, despite the useful clinical evidence of clinical consequences from the previous reviews, the majority of the provided data came from case reports and all reported safety outcomes. Prior reviews focused on safety of herb-drug interactions probably because safety is the primary focus in case reports. These characteristics of the previous review reports, therefore, may pose a threat to the external validity of the provided evidence of the examined herb-drug interactions. Unlike the prior literature, our review included observational studies with different analytical study designs, such as cohort and cross-sectional studies. Additionally, this current review focused on how each of the employed study design and real-world data source can contribute to the herb-drug research and examined studies reporting beneficial and harmful effects. Accordingly, through documenting different types of analytical study designs and data sources, this review provided valuable clinical evidence complemented to the current data of clinical consequences of the combined use of HMs and conventional drugs. A summary illustrating the detailed information of each cited studies in this review, including the corresponding data source, type of study design, herbal medicine and conventional drug being used, potential interactions/main findings, and lastly with potential methodological flaws can be found in Table 3.

5. Future directions for real-world studies

Although current studies have already utilized real-world data to examine herb-drug interactions, there are further areas in which this research application can be improved. A case-control design, a commonly used approach in observational studies, is found not to be employed in herb-drug interaction studies utilizing real-world data in this review [37]. The inherent study limitations and the nature of case-control studies, detailed in Table 2, may significantly limit their utility in drug-herb assessments; however, this kind of design is suitable for investigating rare outcomes, latent outcomes, and multiple exposures [38]. Therefore, when appropriate, case-control studies can still be considered in the future for providing real-world evidence of herb-drug combinations.

As observational studies are prone to confounding and bias, novel approaches such as propensity-score (PS) matching and high-dimensional PS analysis can be considered in future studies to overcome the inherent limitations of real-world studies, such as measured and unmeasured confounding [39,40]. Additionally, novel study designs

Table 3. Evaluation of observational studies assessing herb-drug interactions.

Study	Data source	Study design	Herbal medicine	Conventional drug	Potential interactions/ Main findings	Potential methodological flaws
Hsu et al. [9]	Health insurance claims database	Cohort	*Ginseng*	Tamoxifen	A significant inhibitory relationship between *Ginseng* consumption and subsequent endometrial cancer among breast cancer survivors was found.	- Uncontrolled disease severity - Not specified continuous use of herbal medicine
Wu et al. [10]	Health insurance claims database	Cohort	*Dang-qui*	Tamoxifen	*Dang-qui* consumption is common among breast cancer survivors and seems to decrease the risk of subsequent endometrial cancer.	- Uncontrolled disease severity - Not specified continuous use of herbal medicine
Chan et al. [11]	Health insurance claims database	Cross-sectional	*Ginkgo biloba extract (GBE)*	Antiplatelet or anticoagulant agents	Concurrent use of *GBE* and antiplatelet/anticoagulant agents may increase the risk of bleeding in patients with known bleeding risks and in elderly.	- Uncontrolled dose or duration of herb usage - Random error
Lopatin et al. [13]	Electronic health records	Cohort	*Cyclamen europaeum (CE)*	Respiratory antibiotics (amoxicillin, clarithromycin, etc.)	Both *CE* in monotherapy or added to antibiotics reduced nasal symptoms and chronic rhinosinusitis recurrences compared to antibiotics in monotherapy.	- Confounding of comedications usage - Random error
Thronicke et al. [14]	Electronic health records	Cohort	*Viscum album* L. *(VA, mistletoe) extracts*	Immune checkpoint inhibitors (ICM)	Concomitant use of *VA* may not alter ICM-induced adverse event rates.	- Uncontrolled disease severity - Random error
Jermini et al. [16]	Questionnaire	Cross-sectional	*Herbal medicines (Viscum album, Camellia sinensis, etc.)*	Anticancer treatments (chemotherapy, radiotherapy, etc.)	The prevalence of *Herbal medicines* use during cancer treatment was high (45%). However, only a small percentage of patients had described the use of herbal drugs to their oncologists.	- Random error - Recall bias - Selection bias

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Table 3. (continued)

Study	Data source	Study design	Herbal medicine	Conventional drug	Potential interactions/ Main findings	Potential methodological flaws
Loquai et al. [17]	Questionnaire	Cross-sectional	*Herbal medicines (Mistletoe, Mushroom)*	Melanoma treatments (ipilimumab, interferon, etc.)	Most patients (80%) concomitantly received a melanoma-specific treatment and herbal medicines, and some of them were exposed to potential herb-drug interactions.	- Recall bias - Survival bias - Uncontrolled dose or duration of herb usage
Djuv et al. [18]	Questionnaire	Cross-sectional	*Herbal medicines (Echinacea purpurea, Ginkgo biloba, etc.)*	Conventional drugs (anti-infectives, anticoagulant, etc.)	A high percentage of herbal co-use was observed among patients using conventional drugs in general practice, especially in elderly and chronically ill patients.	- Random error - Recall bias - Selection bias
McLay et al. [19]	Questionnaire	Cross-sectional	*Herbal medicines (Chamomile, Ginseng, etc.)*	Conventional drugs (antibacterials, opiate analgesics, etc.)	Concurrent use of herbal products and prescription medicines during pregnancy was common and carried potential risks.	- Uncontrolled dose or duration of herb usage - Recall bias - Non-response bias
Mohammadi et al. [20]	Survey and electronic health records	Cross-sectional	*Herbal medicines (Ginseng, Ginkgo, etc.)*	Conventional drugs (aspirin, clopidogrel, etc.)	The prevalence of herbal supplement usage among CKD patients was 18.6%. In the study, ginseng had the most possible interactions with prescription drugs.	- Recall bias - Selection bias - Uncontrolled disease severity
Levy et al. [21]	Survey and electronic health records	Cross-sectional	*Herbal medicines (Sage, Chamomile, etc.)*	Conventional drugs (methadone, simvastatin, etc.)	One in 55 hospitalizations may have adverse events associated with herb-drug interactions, which may worsen existing medical conditions.	- Recall bias - Selection bias - Survival bias
Ting et al. [22]	Survey and electronic health records	Cross-sectional	*Herbal medicines (Aloe, Ginseng, etc.)*	Digoxin	Few patients took herbal medicines that could interact with digoxin, and no clinically significant herb-digoxin interactions were observed.	- Random error - Recall bias - Selection bias

Peltzer et al. [23]	Survey and electronic health records	Cross-sectional	*Herbal medicines (St. John's wort, Cannabis, etc.)*	Antiretrovirals	Traditional herbal therapies were commonly used by HIV treatment naïve outpatients of public health facilities in South Africa.	- Recall bias - Selection bias
Chi et al. [24]	Survey and electronic health records	Cross-sectional	*Herbal medicines (Ginkgo, Licorice, etc.)*	Conventional drugs (anticoagulants, antiplatelets, etc.)	Among elderly participants who used any herb and drug combinations, 43.3% were exposed to at least one potential herb-drug interactions. Most of them were related to herbs with anticoagulant/antiplatelet properties.	- Selection bias - Survival bias
Levy et al. [25]	Survey and electronic health records	Cross-sectional	*Herbal medicines (Sage, Chamomile, etc.)*	Anesthetics and antithrombotic drugs	This study found that 44% patients used herbal supplements. Of these, 16.5% of the herb usage could potentially interact with anesthesia and 10% of them could potentially interact with antithrombotic drugs.	- Recall bias - Selection bias - Survival bias - Uncontrolled dose or duration of herb usage
Drozdoff et al. [26]	Survey and electronic health records	Cohort	*Herbal medicines (St John's wort, Mistletoe, etc.)*	Gynecological cancer therapy (taxane, anti-HER2, etc.)	There was overall high (74%) use of biologically based complementary and alternative medication in cancer patients undergoing systemic therapy. However, only 1 patient seemed to be exposed to a potential clinically relevant herb-drug interaction.	- Random error - Recall bias - Selection bias - Uncontrolled dose or duration of herb usage

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Table 3. (continued)

Study	Data source	Study design	Herbal medicine	Conventional drug	Potential interactions/ Main findings	Potential methodological flaws
Jaradat et al. [27]	Survey and electronic health records	Cross-sectional	*Herbal medicines (Sage, Anise, etc.)*	Conventional drugs (metformin, insulin, etc.)	Use of medicinal herbs was prevalent (59%) among Palestinian patients attending primary healthcare centers. Patients with potential herb-drug interactions were older, having a higher mean number of chronic diseases and medications.	- Recall bias - Selection bias - Uncontrolled dose or duration of herb usage
Levy et al. [28]	Survey and electronic health records	Cross-sectional	*Herbal medicines (Chamomile, Ginger, etc.)*	Conventional drugs (antithrombotics, quinolones, etc.)	Approximately half patients took *herbal medicines* during hospitalizations. Of them, 47% had at least one potential herb-drug interaction.	-Recall bias -Selection bias -Survival bias
Leung et al. [29]	Survey and electronic health records	Cross-sectional	*Complementary and Alternative Medicine; CAM (Ginkgo biloba, Ginseng, etc.)*	Warfarin	Around one-third of patients used CAM products with the potential to interact with warfarin. The exposure to CAM was not associated with an increased risk of self-reported bleeding in patients receiving warfarin.	- Random error - Recall bias - Confounding of comedications usage - Vaguely defined duration of herb usage

such as nested case-control study [33], case-crossover study [32], case-time control study [32], and self-controlled case series [41], as well as new user design coupled with an active-comparator analysis [42], are currently all unused in herb-drug interaction research. These designs and methods can also be considered as potential means to mitigate bias and confounding. Overall, there is an unmet need for understanding interactions between HM and conventional drug in present clinical settings primarily due to the limited evidence, thus the implementation of newer or rigorous methodologies may help bring herb-drug related research to the next level. As the real-world evidence on the actual interactions between HMs and conventional drugs are currently scarce, future findings generated from these new approaches may provide important insights on the combined use of HMs with conventional drugs in terms of the beneficial or the harmful effect of herb-drug combinations in daily clinical practice.

6. Conclusions

Despite the limitations discussed in this review paper, studies that utilized observational methodologies via different data sources and study designs still reported informative findings regarding the interactions between HM and conventional drug. Depending on the types of real-world data used, the aforementioned studies provided various information on the harmful and beneficial effects of co-using HMs and conventional drugs, and the prevalence of potential herb-drug interactions. With the lack of RCTs being conducted on herb-drug interactions primarily due to ethical considerations, observational studies can step in and provide supporting evidence to complement future RCTs and help to confirm whether current herb-drug interaction findings reported in animal and *in vitro* research can be translated to real-life settings. With a continuous improvement in controlling and mitigating confounding and bias, well-regulated and appropriately designed studies that utilize real-world data can serve as a useful tool in making significant contributions to improve the knowledge about the clinical consequences of herb-drug consumption, and help healthcare professionals to reinforce the herb-drug use where benefits are found and to prevent co-consumption where risks are observed.

Conflict of interest

The authors declare no conflict of interests.

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