



Systematic Review

Does *Angelica Sinensis* (Dang-qui) Increase the Risk of Breast Cancer? A Systematic Review



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Abstract

Background and objecties: *Angelica sinensis* (Dang gui) has been widely used in traditional Chinese medicine (TCM) clinics and diet therapy for thousands of years. According to TCM theory, *A. sinensis* can be used for the treatment of breast cancer. As *A. sinensis* has effects on estrogen, it may have an adverse effect on the prognosis of breast cancer. This article systematically reviews the literature to explore whether breast cancer patients need to avoid taking *A. sinensis*.

Methods: Using the search terms “breast cancer AND Dong-quai”, “breast cancer AND *Angelica sinensis*”, “breast cancer AND Dang gui” and “breast cancer AND Dang qui”, relevant studies were retrieved from the PubMed database up to December 31, 2022. After excluding irrelevant and repeated studies, the papers were critically reviewed by TCM physicians, and the papers were secondly screened by the impact factor and ranking of the published journals. The included papers were classified into three groups, reporting a “positive”, “negative” or “inconclusive” effect in patients with breast cancer.

Results: A total of 22 articles were identified, which included 9, 5 and 7 positive negative and inconclusive studies, respectively. The results showed that studies advocating that *A. sinensis* may be safely consumed by patients with breast cancer had a higher evidence hierarchy than those that did not support consumption.

Conclusions: The findings implied that *A. sinensis* can be prescribed to patients with breast cancer in appropriate doses under TCM treatment theory.

Introduction

Angelica sinensis (commonly known as *Dong-quai*, *Dang gui*, *Dang-qui*) is a Chinese herb that had been widely used in Traditional Chinese Medicine (TCM) to treat blood-related diseases for thousands of years.^{1,2} Many TCM herbal formulas contain *A. sinensis*, an important ingredient in diet therapy.³ However, in several cancer centers, patients with breast cancer are advised not to take *A. sinensis* during the treatment of cancer due to the herb possessing estrogenic-like effects. An estrogenic effect was considered to be a risk factor for breast cancer.⁴ Some studies showed that *A.*

sinensis at high doses may stimulate the growth of breast cancer cells.^{5,6} Therefore, avoiding the use of *A. sinensis* by patients with breast cancer seems to be a reasonable medical decision.

On the other hand, some studies showed a different point of view. An extract of *A. sinensis* has been shown to bind to the human estrogen receptor, the binding was very weak, and could easily be replaced by other ligands. Thus, it was reported as inactive, with no significant effect in patients with breast cancer.⁷ *Angelica* polysaccharides have been demonstrated to have potential as a useful therapeutic agent for the treatment of breast cancer.^{8,9} Analysis of a population-based database by Lai and colleagues found that a herbal formula that contains *A. sinensis* is the most common TCM prescribed for patients with breast cancer.¹⁰ *A. sinensis* has been widely used in diet therapy, and TCM practitioners often use it to treat patients with breast cancer. Another study showed that among patients treated with tamoxifen, a selective estrogen receptor modulator, those who consumed Chinese herbal products containing *A. sinensis* were noted to have a lower subsequent endometrial cancer risk than those who had never used Chinese herbal products. The results showed that the estrogenic activity of the herb did not significantly induce the proliferation of

Keywords: *Angelica sinensis*; Dang-qui; breast cancer; traditional Chinese medicine.

Abbreviations: BP, N-Butylidenephthalide; TCM, traditional Chinese medicine.

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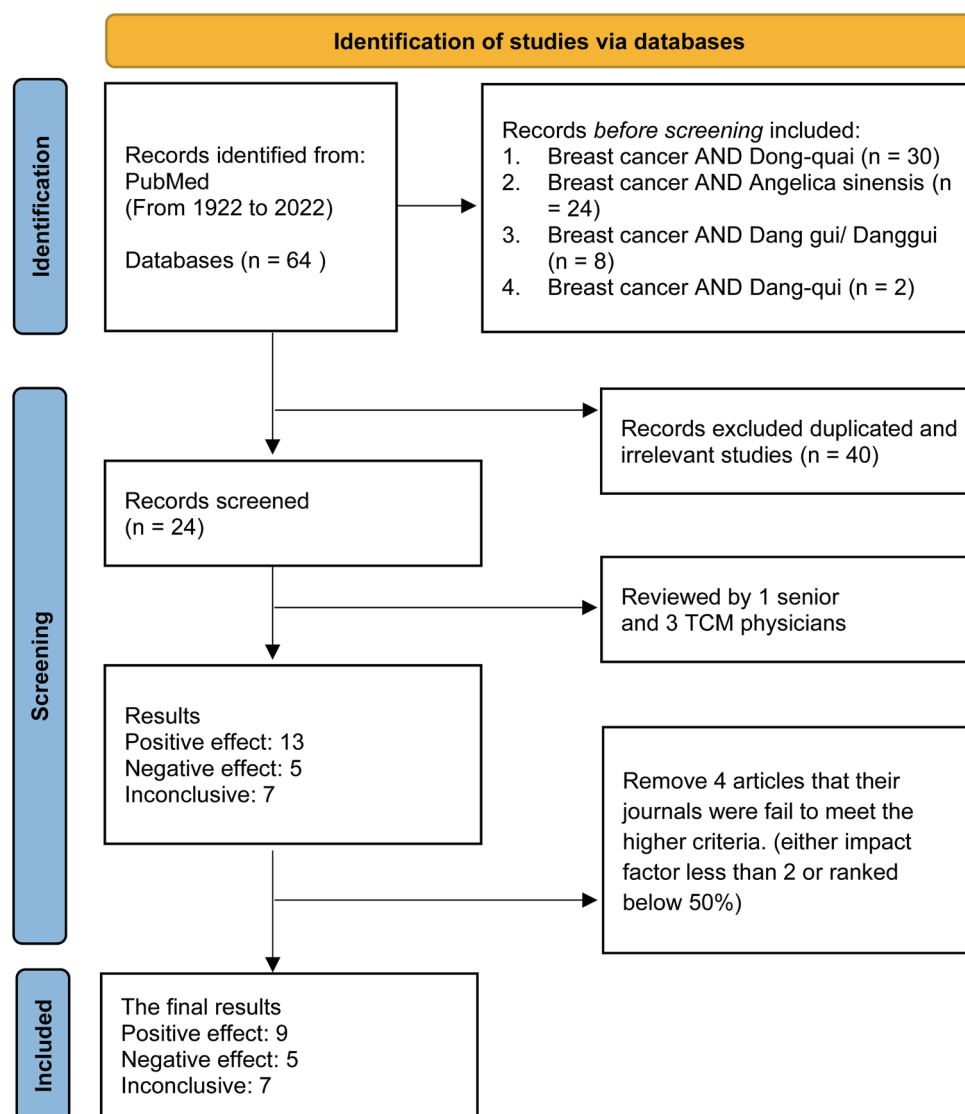


Fig. 1. Flow chart of literature assessment.

breast cancer cells.¹¹ According to a review of the literature *A. sinensis* consumption has no negative interaction with conventional tamoxifen treatment in patients with breast cancer.¹²

As the impact of taking *A. sinensis* is still controversial in patients with breast cancer, the present study aimed to investigate whether patients need to avoid *A. sinensis* consumption based on evidence from a systematic review of the literature.

Methods

In order to explore the risk of *A. sinensis* on breast cancer, we searched the PubMed database and used Boolean operators to narrow the search results to relevant studies. As *A. sinensis* has several synonyms, the search employed the terms including “breast cancer AND Dong-quai” or “breast cancer AND Angelica sinensis” or “breast cancer AND Dang gui/ Danggui” or “breast cancer AND Dang-qui” to retrieve all studies in PubMed published up to December 2022. After excluding duplicate and irrelevant studies, the

articles identified from PubMed were reviewed by three physicians from the Department of Chinese Medicine in our hospital. To evaluate whether *A. sinensis* has a risk effect in patients with breast cancer, the three physicians classified the results of the studies into three groups: those reporting a “positive”, “negative”, or “inconclusive” effect. When the classification was inconsistent among the three physicians, the article was then further reviewed by a senior Chinese medicine physician to make the final judgement. To obtain a higher quality of screening literatures, we further set second criteria for screening papers’ conditions. The *in vitro*, systemic review and retrospective cohort study with literature screening conditions were further refined according to the journal’s previous year’s impact factor as greater than 2.0, and the field ranked in the top 50% as a condition for acceptance. The screening conditions for the randomized control trials were based on the Jadad Quality Score, with greater than 3 as a condition.¹³ The process of search, exclusion criteria, and rating of the evidence hierarchy are shown in Figure 1.

Evidence-based medicine is primarily based on valuable infor-

mation that is extracted from a systematic review process, in which relevant studies are critically appraised by experts and the hierarchy of evidence is rated into different classes, from high to low, in the following categories: expert opinion, case series/case report, case-control study, cohort study, randomized controlled trial, and systematic review.^{14,15} In the systematic review process, a biostatistics approach is used to combine the results of different studies, and meta-analysis is then employed to consolidate a quantitative review; a final summary of the *post hoc* analysis is often presented as a chart, known as a forest plot.^{16,17}

Our study aimed to investigate the estrogenic activity of *A. sinensis* and assess whether it may affect the prognosis of patients with breast cancer. Thus, using a quantitative review approach, we first critically reviewed the articles that fitted our criteria, and classified the studies into those concluding a “positive”, “negative”, or “inconclusive” effect on patients with breast cancer, then displayed the outcomes with an improved forest plot. Additionally, the evidence hierarchy on the vertical axis includes “animal research/*in vitro* study” as an item to emphasize the importance of this type of study, and either the article number or the impact factors of the published journals are shown on the horizontal axis. In this way, article number, hierarchy of evidence, and impact factor are combined to weigh those studies with highly reliable findings. We refer to this type of improved plot as a quantitative forest plot, and used it to present the results of our analysis.

Results

After the search had been executed in PubMed, up until December 31, 2022, the search terms “breast cancer AND Dong-quai”, “breast cancer AND *Angelica sinensis*”, “breast cancer AND Dang gui/ Danggui” and “breast cancer AND Dang-qui” identified 30, 24, 8, and 2 articles, respectively. In the 64 articles identified, the manual removal of duplicates and irrelevant studies left a total of 21 articles for further analysis.^{5–8,10,12,18–28}

The relevance of each study was summarized based on the publication year, authors, title, journal, research type/evidence level, and conclusion. Among them, nine articles reported that *A. sinensis* has a positive effect on patients with breast cancer, as listed in Table 1,^{6,12,18,19,21,28–31} and five articles reported a negative effect, as listed in Table 2.^{5,22,23,32,33} Additionally, one article concluded no effect;²⁴ another suggested that *A. sinensis* has both positive and negative effects;²⁵ and the remaining two discussed other topics.^{26,27}

There were nine positive studies, six of which were *in vitro* experiments, one is a retrospective cohort study, one is a system review, and the last one is a random distribution test. Only six studies met the screening criteria and have been plotted. Five articles reported a negative effect and all met the screening criteria. The results of the analysis of studies classified based on effect and evidence hierarchy were plotted as quantitative forest plots (Fig. 2).

Discussion

Breast cancer has a very high incidence in women worldwide. Patients with breast cancer normally choose Western medicine as the first line of treatment. Due to the side effects of surgery, chemotherapy and radiation therapy, many patients seek assistance from complementary medicine. In Taiwan, a study by Lai and colleagues showed that 81.5% of newly-diagnosed patients with breast cancer sought help from a TCM clinic at least once.¹⁰ With such a high usage rate, determining the effect and safety of Chi-

nese herbs in patients with breast cancer is even more important. In recent years, the media have reported that *Angelica* consumption may increase breast cancer cell growth, which has made patients with breast cancer afraid to take *A. sinensis*. When breast cancer patients receive treatment in Western medicine clinics, they are often told to avoid *A. sinensis*. In order to address this current controversial issue, we performed a systematic review of relevant recent studies identified from the PubMed database and analyzed the results of the studies to determine the effect of *A. sinensis* on patients with breast cancer based on scientific evidence. We have listed the information of each study, including the journal name, research type, and key conclusion; to assist readers in terms of saving time in researching and interpreting the literature. The main feature of this study was the analysis of the results of studies that fitted our study criteria, plotting the results into quantitative forest plots based on the evidence hierarchy, and the reported positive or negative effects on patients with breast cancer. In this way, readers can easily understand whether *A. sinensis* consumption is suitable for breast cancer patients from our analysis. For example, Figure 2 shows that studies in the category of animal research/*in vitro* study are clearly dominant in terms of the number of papers and evidence hierarchy. The analysis results presented via a quantitative forest plot differ from a conventional literature review, as the former gives researchers a clear indication of the pros and cons of the argument based on the evidence hierarchy.⁷

In the literature identified from PubMed, three *in vitro* studies employed cell-based experiments, and showed that *A. sinensis* increased cell proliferation of MCF-7 breast cancer cells.⁸ Whether or not this effect occurs through stimulation of estrogen receptors, the argument is made in the studies, and further investigation is needed. Another *in vitro* study, however, found that *A. sinensis* polysaccharide can promote apoptosis in breast cancer cells. Two studies published in 2001 investigated the estrogenic activity of *A. sinensis*; one reported that *A. sinensis* possesses antiestrogenic activity,²⁰ and the other suggested that an extract of *A. sinensis* can bind to the estrogen receptor, but with only a weak binding affinity.⁶ A review article published in 2003 summarized that although whether or not *A. sinensis* possesses estrogenic activity remains controversial, it can be concluded that *A. sinensis* is inactive in terms of binding to the human estrogen receptor due to a low binding affinity.⁷ The effects of phytoestrogens on breast cancer require more research for validation. No single mechanism can explain the effect of endogenous and exogenous estrogens. A randomized, double-blind, placebo-controlled study showed that administration of a Chinese medicinal herb complex that contained *Ganoderma tsugae* (Lingzhi), *Codonopsis pilosula* (Dang shen), and *A. sinensis* to patients receiving chemotherapy/radiotherapy delayed or eased the leucocyte and neutrophil reductions that usually occur during cancer therapy, as well as improved the immunity of the patients.²¹

The three most recent studies were performed in 2017 and 2018. Two studies performed in 2017 are both relevant to Z-ligustilide, a major compound obtained from *A. sinensis*. One study demonstrated that Z-ligustilide sensitized tamoxifen-resistant MCF-7 cells to apoptosis through a caspase-mediated pathway and augmented the tamoxifen-induced DNA damage;¹⁹ the other study suggested that Z-ligustilide acts as a novel epigenetic modulator and could be developed as a new treatment strategy for tamoxifen-resistant breast cancer.¹⁸ The study performed in 2018 indicated that *Radix Angelica Sinensis* had a component N-Butylidenephthalide (BP), which can induce apoptosis in breast cancer cells.

The three aforementioned studies that proposed that *A. sinensis* has a negative effect on patients with breast cancer were all *in vitro* studies, while those that demonstrated *A. sinensis* to have a

Table 1. Literature from PubMed reporting that *A. sinensis* may have a positive effect on patients with breast cancer

No.	Authors	Title	Journal	Publication year	Study type	Conclusion
1	Liu J <i>et al.</i> ⁶	Evaluation of the estrogenic activity of plant extracts for the potential treatment of menopausal symptoms	<i>J Agric Food Chem.</i>	2001	<i>In vitro</i>	<i>A. sinensis</i> has a weak estrogenic binding ability and induction effect on the progesterone receptor and presenilin-2 mRNA expression.
2	Zhuang <i>et al.</i> ²¹	Effects of a Chinese medical herbs complex on cellular immunity and toxicity-related conditions of breast cancer patients	<i>Br J Nutr.</i>	2012	Randomized controlled trial	The intervention of a Chinese medicinal herb complex (<i>Ganoderma tsugae</i> , <i>Codonopsis pilosula</i> , and <i>A. sinensis</i>) can delay or ease the reduction of leucocyte and neutrophil levels that often occur in patients during breast cancer treatment.
3	Wu <i>et al.</i> ¹²	The prescription pattern of Chinese herbal products that contain dang-qui and risk of endometrial cancer among tamoxifen-treated female breast cancer survivors in Taiwan: a population-based study	<i>PLoS One.</i>	2014	Retrospective cohort study	According to the National Health Insurance Research Database, <i>A. sinensis</i> consumption was negatively correlated with the risk of subsequent endometrial cancer.
4	Qi <i>et al.</i> ¹⁹	Sensitization of tamoxifen-resistant breast cancer cells by Z-ligustilide through inhibiting autophagy and accumulating DNA damage	<i>Oncotarget.</i>	2017	<i>In vitro</i>	Z-ligustilide, a major phthalide compound obtained from <i>A. sinensis</i> , can sensitize tamoxifen-resistant breast cancer cells, suggesting that <i>A. sinensis</i> has potential as a novel autophagy inhibitor to overcome chemoresistance.
5	Ma <i>et al.</i> ¹⁸	Z-ligustilide restores tamoxifen sensitivity of ERα negative breast cancer cells by reversing MTA1/IF116/HDACs complex mediated epigenetic repression of ERα	<i>Oncotarget.</i>	2017	<i>In vitro</i>	Z-ligustilide, the key compound in the volatile oil of <i>A. sinensis</i> , acts as an epigenetic modulator and restores breast cancer cell sensitivity to tamoxifen. The findings suggest that <i>A. sinensis</i> has critical clinical applications for breast cancer chemoprevention and therapy.
6	Su <i>et al.</i> ²⁸	Anti-Tumor and Radiosensitization Effects of N-Butylidenephthalide on Human Breast Cancer Cells	<i>Molecules.</i>	2018	<i>In vitro</i>	There is a potential chemotherapeutic and radio-sensitizing agent in <i>A. sinensis</i> to treat breast cancer called N-Butylidenephthalide (BP), which can induce apoptosis in breast cancer cells.
7	Wu and Chen <i>et al.</i> ²⁹	Riboflavin immobilized Fe3O4 magnetic nanoparticles carried with n-butylidenephthalide as targeting-based anticancer agents	<i>Artificial cells, nanomedicine, and biotechnology.</i>	2019	<i>In vitro</i>	n-Butylidenephthalide (BP) is a potential anticancer drug extracted from <i>Angelica sinensis</i> . In this study, riboflavin-5'-phosphate (RFMP)-immobilized iron oxide magnetic nanoparticles (Fe 3 O 4 MNPs) were used as carriers of BP to treat cancer cells from liver, prostate, and breast cancer. Cell viability using BP-immobilized Fe3O4@RFMP MNPs was two-fold lower than that achieved using a similar amount of free-form BP. We assessed the levels of cysteine-aspartic proteinase 3 (caspase 3) in cell lysates obtained after BP-Fe treatment in 3O4@RFMP MNPs to demonstrate that apoptosis is primarily involved in target cell growth inhibition.
8	Chen, <i>et al.</i> ³⁰	A population-based case-control study on the association of <i>Angelica sinensis</i> exposure with risks of breast cancer	<i>Journal of Traditional and Complementary Medicine.</i>	2020	Database	The researchers conducted a population-based case-control study in which all newly diagnosed breast cancer patients were included as a case group (n = 34,262). There was a weak but significant protective effect against breast cancer with angelica use (adjusted odds ratio (aOR) 0.95, 95% (CI) 0.93–0.98), with a significant dose gradient relationship. The seemingly protective effect of angelica was found to be more pronounced in first-time diagnosis women aged 47-55 (aOR 0.93, 95% CI 0.88–0.98).
9	Li, and Shi ³¹	Therapeutic effects and mechanism of ferulic acid and icaritin in mammary gland hyperplasia model rats via regulation of the ERK pathway	<i>Annals of Translational Medicine.</i>	2021	<i>In vivo</i>	Ferulic acid (FA) and icaritin (ICA) are active compounds in <i>Angelica</i> and <i>Epimedium</i> , respectively. The compounds also block pathological changes in MGH, including the number of breast lobules, and hyperplasia or dilation of acini and ducts.

No 1–6 meet the higher criteria of second screening.

Table 2. Literature from PubMed showing that *A. sinensis* (*Dang qui*) may have a negative effect on patients with breast cancer

No.	Authors	Title	Journal	Publication year	Study type	Conclusion
1	Amato <i>et al</i> . ⁵	Estrogenic activity of herbs commonly used as remedies for menopausal symptoms	<i>Menopause</i> .	2002	<i>In vitro/ in vivo</i>	A high <i>A. sinensis</i> dose stimulates the growth of MCF-7 breast cancer cells independent of estrogenic activity. The treatment had no effect on uterine weight <i>in vivo</i> when administered orally to ovariectomized mice.
2	Lau <i>et al</i> . ²³	Use of <i>dong-quai</i> (<i>Angelica sinensis</i>) to treat peri- or postmenopausal symptoms in women with breast cancer: is it appropriate?	<i>Menopause</i> .	2005	<i>In vitro</i>	The water extract of <i>A. sinensis</i> stimulated MCF-7 breast cancer cell proliferation with weak estrogen-agonistic activity and increased the growth of BT-20 breast cancer cells independent of pathways via the estrogen receptor.
3	Chang <i>et al</i> . ²²	Modulation of HER2 expression by ferulic acid on human breast cancer MCF7 cells	<i>Eur J Clin Invest</i> .	2006	<i>In vitro</i>	Ferulic acid, an active compound derived from <i>A. sinensis</i> , can induce cell proliferation of several human breast cancer cell lines by promoting the expressions of HER2 and ERα.
4	Zhu <i>et al</i> . ³²	Tumorigenic risk of <i>Angelica sinensis</i> on ER-positive breast cancer growth through ER-induced stemness <i>in vitro</i> and <i>in vivo</i>	<i>Journal of Ethnopharmacology</i> .	2021	<i>In vitro/ in vivo</i>	In this study, the tumorigenic effect of <i>Angelica sinensis</i> (AS) aqueous extract on the growth of estrogen receptor (ER) positive breast cancer was investigated by <i>in vitro</i> and <i>in vivo</i> ER-induced stem cells. AS showed tumorigenic potential for ER-positive BC growth through ERα-induced stemness, suggesting that AS is not recommended for breast cancer in terms of safety.
5	Yen <i>et al</i> . ³³	Interactions between natural products and tamoxifen in breast cancer: a comprehensive literature review	<i>Frontiers in Pharmacology</i> .	2022	Review	Various <i>in vitro</i> and <i>in vivo</i> studies have shown that the combination of natural products and TAMs produces synergistic anticancer effects, including improved inhibition of tumor cell growth and TAM sensitivity, and reduced TAM side effects or toxicity. In contrast, some natural products, including <i>Angelica sinensis</i> (Oliv.) Diels (Apiaceae), exhibit estrogen-like activity, which may reduce the anticancer effects of TAMs.

positive effect were of different study categories, including cohort study, randomized controlled trial and systematic review. Therefore, we concluded that there exists more evidence to indicate that *A. sinensis* has a positive effect on patients with breast cancer. Additionally, most of the studies that reported a positive effect were published within the past 10 years, while all those reporting a negative effect were published prior to 2006. This suggests that increasingly, research supports that *A. sinensis* consumption does not increase breast cancer growth, and indicates that the use of *A. sinensis* in patients with breast cancer does not destructively impact the treatment provided by Western medicine.

In the current study, the number of studies that showed *A. sinensis* has a positive effect on patients with breast cancer was greater than those that reported a negative effect, and the evidence hierarchy of the former was also higher than the latter. As *A. sinensis* is a commonly used and important herb in traditional Chinese medicine, it is often prescribed to patients and the amount used is largely dependent on the disease. As many herbs are used in Chinese medical herbs complexes, the interactions between the herbs are complicated, and an extract of a single herb cannot validate the effect of a herb complex. Therefore, if *A. sinensis* is of benefit to patients with breast cancer based on the patient's physical and disease characteristics, a qualified Chinese physician should not particularly avoid prescribing the herb.

In cancer care, conventional Western medicine is normally used as the mainstream treatment. Although complementary/alternative therapies are gradually being accepted and integrated into the treatment strategy for cancer therapy in the present healthcare system, there is often conflict when patients use complementary/alternative therapies during Western medicine treatment.³⁴ The issue that the present study aimed to resolve is a practical example of a similar problem. Clinically, patients with breast cancer suffer from low hemoglobin due to chemotherapy. TCM physicians will use *Si Wu Tang*, a formula containing *A. sinensis*, as the key ingredient, to treat these patients and good results have been obtained in the past. Numbness in the hands and feet often occurs in patients with breast cancer after chemotherapy or radiation therapy. This therapy-associated peripheral neuropathy may take six months to several years to disappear. Modern medicine does not have a good method by which to manage this problem, while *Dang Gui Si Ni Tang* can shorten the course of numbness in the lower extremities.³⁵ However, patients under conventional breast cancer treatment in hospitals are often told to avoid *A. sinensis*, leading to them fearing consumption of the herb and suffering pain as a side-effect of treatment. Based on the results of this study, evidence-based studies have demonstrated that the concept of avoiding *A. sinensis* is outdated and inappropriate.

From clinical experience, there are two main types of *A. sinensis* used in breast cancer. First, one is to reduce the side effects of anti-hormone therapy. Secondly, to reduce hypoglycemia due to the side effects of chemotherapy. More randomized controlled trials are needed to examine these clinical observations. Based on traditional Chinese medicine theory, and with reference to the latest medical evidence, appropriate use of *A. sinensis* will not affect the prognosis of breast cancer. Educating patients with breast cancer to avoid the herb is improper because of the patient's health.

Through systematic review and quantitative analysis of relevant studies, we have summarized the most up-to-date and accurate information. In clinical practice, when patients have a problem with TCM, we recommend that the attending physician consults a TCM practitioner to assist the patient to overcome difficulties during treatment. In most medical fields, when Western medicine physicians need to make certain medical decisions involving comple-

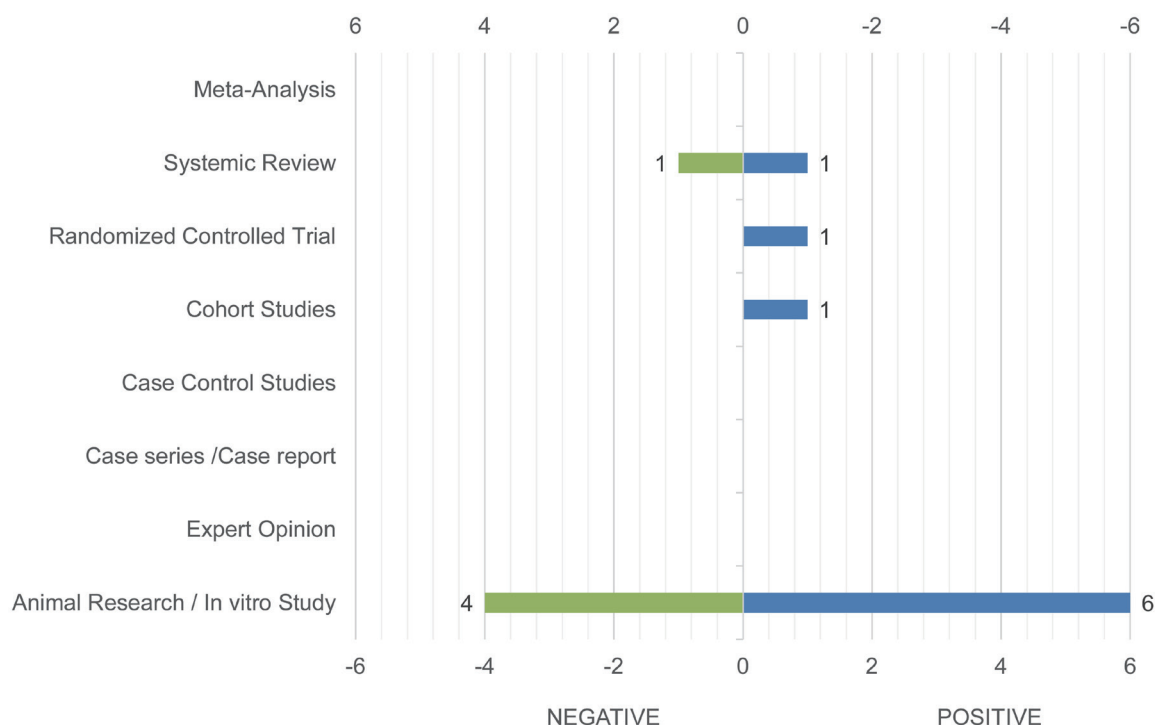


Fig. 2. Quantitative forest plot of studies from PubMed. *A. sinensis* may have positive and negative effects on patients with breast cancer. The vertical axis shows the evidence hierarchy, and the horizontal axis shows the number of papers reporting positive or negative effects.

mentary medicines, it is better to seek advice from professionals and experts of the discipline in order to provide the most benefit to the patient. In recent years, the growing integration of complementary medicine into conventional biomedical health care indicates that the demand for the use of alternative medicine is rising. Up-to-date dialogue between disciplines for the treatment of cancer, a complicated disease with broad aspects, and integration of complementary medicine into conventional medicine are warranted.³⁶ Integrative oncology is also urgently needed.^{37,38}

There were limitations in this study. For example, the number of relevant studies was small, and many had a low evidence hierarchy. In addition, the keywords used in the PubMed search also limited the aspect of our study. Several papers focused on the estrogenic effects of *A. sinensis* and further discussed its impact on patients with breast cancer. These papers were excluded from our study as they did not fit our criteria. This issue may be improved in future studies that employ different criteria. From the perspective of TCM, the principle of using Dang Gui in breast cancer patients should still be administered according to the method of pattern differentiation and treatment. Dang Gui can be used when the patient presents with a pattern of blood deficiency, with the typical dosage ranging from 9 to 15 grams. Particularly after radiotherapy and chemotherapy for breast cancer, patients often exhibit patterns of liver blood deficiency, in which case a prescription with Dang Gui as the primary ingredient should be used. However, if the patient does not have blood deficiency or even shows significant signs of heat, Dang Gui should not be used in any way.

Conclusion

This study contends that *Angelica sinensis* is not harmful to the prognosis of breast cancer, and is even slightly helpful. However,

since there is literature supporting that *A. sinensis* is harmful to breast cancer, the data can only be faithfully presented, mainly to provide a reference for medical decision-making. Medical personnel and patients can take into account their individual situations to make the most beneficial decision for the patient. This is the stance of this research institute. The causes of breast cancer are complex. Age, genetics, diet, lifestyle, habits, menstruation, pregnancy history, and medication all affect the occurrence of the disease and can cause experimental anomalies. Therefore, due to the limit of both the sample number and the evidence hierarchy, more large-scale research is required in the future to ensure the safety of using *A. sinensis* in patients with breast cancer.

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Conflict of interest

Mark C. Hou served as the editorial board member of *Future Integrative Medicine* from 2021 to 2022. All authors confirm that they do not have any conflict of interests regarding to the publication of this manuscript.

Author contributions

Study design and writing (MCH), execution and drafting the manuscript (YLC), diagrams and proofreading (YFH).

Data sharing statement

The data used in support of the findings of this study are available from the corresponding author upon request.

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