


# Potential Interactions of Biologically Based Complementary Medicine in Gynecological Oncology

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## Abstract

**Objective.** The aim of this study was to assess the potential risks of interactions between biologically based complementary and alternative medication (BB-CAM) and conventional drugs during systemic therapy in breast and gynecological cancer patients by analyzing the actual CAM-drug combinations from individual patients' records. **Methods.** From September 2014 to December 2014 and from February 2017 to May 2017, all patients (n = 717) undergoing systemic therapy at the Gynecologic Oncology Day Care Unit in the Gynecology and Obstetrics Department of the Technical University of Munich, Germany, were asked to participate in a questionnaire about all their medications. To assess the potential risk of CAM-drug interactions (CDIs), we initially utilized the Lexicomp drug interaction database. This assessment was then expanded with a systematic search of other digital databases, such as the National Center for Complementary and Integrative Health, Memorial Sloan Kettering Cancer Center, PubMed, and MEDLINE as well as the Cochrane Library. **Results.** Among 448 respondents, 74.1% reported using BB-CAM simultaneously with their systemic therapy. The assessment showed 1 patient with a potentially clinically relevant CDI, where the interaction was based on a self-medicated combination of Echinacea and cyclophosphamide. Furthermore, 81 patients (18.1%) were thought to have interactions because of a combination of BB-CAMs and cytochrome P450 3A4-metabolized anticancer drugs. **Conclusions.** Our data demonstrated high overall use of BB-CAMs by cancer patients undergoing systemic therapy. The analyses showed only 1 clinically relevant CDI.

## Keywords

complementary and alternative medicine, CAM, herb-drug interaction, supplement-drug interaction, chemotherapy, oncology, cancer

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## Introduction

Patients frequently turn to complementary and alternative medicine (CAM), and especially in the past decades, biologically based complementary medication (BB-CAM) has become increasingly popular as a common self-medication tool.<sup>1–5</sup> A European survey revealed a CAM user rate of about 36% among cancer patients.<sup>6</sup> Looking at CAM user characteristics, the data show that female gender, young age, higher educational level, and nonmetastatic disease are more often associated with CAM use.<sup>7,8</sup> Accordingly, Navo et al<sup>9</sup> analyzed the use of complementary medication in breast and gynecological cancer patients, and they found that 48% of the patients used some kind of CAM treatment—for example, herbs and megavitamins/minerals. Research suggests that there are various reasons why cancer patients opt for health approaches outside the sphere of

conventional medical care. Some patients use CAM to mitigate disease- or treatment-related symptoms or improve quality of life, whereas others hope for an additional effect on antineoplastic treatment, cancer-preventive properties, or proimmune activity, and some want more control over and responsibility for their own care.<sup>8,10–12</sup>

There are, however, several reasons why some patients do not take CAM: missing communication about CAM, poor

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clinical evidence of adverse effects on cancer therapy, probable side effects, and the risk of interactions between CAM and conventional medication (CAM-drug interactions [CDIs]). Nonetheless, the overall number of CAM users is high, especially among cancer patients.<sup>1,7,8,13</sup>

The International Society for Integrative Oncology (SIO) released guidelines in 2009 recommending that CAM use should be evaluated prior to starting cancer treatment to assess the appropriateness of continued use during treatment.<sup>14</sup> Therefore, various websites have emerged in the past decade to evaluate the risk of CDIs. To rate available websites, McDermott et al<sup>15</sup> conducted a pilot study, which advised health care practitioners to use more than 1 website to assess the potential efficacy and safety of CAM.<sup>15</sup> Former studies investigating CDIs reported a large difference in the number of interactions. The many different CDI assessment methods could be one reason. For instance, McCune et al<sup>16</sup> reported that 27% of the patients were at risk of clinically significant CDIs<sup>16</sup>; Zeller et al<sup>17</sup> suggested that the number was one-third of all participants<sup>17</sup>; and Ramos-Esquivel et al<sup>18</sup> found that a full 90% of the participants were at risk. Prior research proposes a high rate of potential CDIs among cancer patients and, thus, an omnipresent risk of negative effects from CAM use. Health care professionals should not fail to effectively advise their patients regarding CAM use. Therefore, the aim of this study was to assess potential BB-CAM–drug interactions during systemic therapy among breast and gynecological cancer patients.

## Methods

### *Patient Characteristics and Survey*

We obtained detailed information about the individual use of BB-CAM through a cross-sectional descriptive survey. From September 2014 to December 2014 and from February 2017 to May 2017, a self-administered 8-item questionnaire was handed out to all patients undergoing systemic therapy at the chemotherapy unit of the Department of Gynecology and Obstetrics, Technical University of Munich, Klinikum rechts der Isar, Munich, Germany (n = 717). More details about the creation and the process of the survey can be found in a former study, which dealt with a different scientific issue.<sup>19</sup> The survey is given in Supplementary File 1. Conventional comedications and complementary medications were recorded by the patients. Participation in the study was voluntary. By filling out the questionnaire, the patients gave their consent to the survey and collection of personal data. Two separate time frames (2014 and 2017) were chosen to detect possible trends in use and characteristics of BB-CAM use. Routinely prescribed supportive medication, such as vitamin D or calcium supplements, were excluded from the analysis. Patients' cancer diagnosis and complete medical history, including former and

current cancer therapy, were documented by the treating physician.

A total of 448 patients were included in this study. Patients' age as well as disease- and therapy-related characteristics are listed in Table 1. With the exception of 1 man, all patients were women. Various combinations of more than 1 systemic cancer therapy per patient were possible.

### *Assessment of Potential BB-CAM–Drug Interactions*

The combinations of BB-CAM and systemic cancer therapy was first assessed via the computerized interaction database system Lexi-Interact in Lexicomp.<sup>20</sup> In the Lexicomp database, 1 separate monograph has been introduced for each herb-drug interaction, which classifies them based on their risk rating, severity, and documentation reliability rating. It is a publicly accessible international database, which is well known to health professionals and also gives a brief presentation of the published data. The Lexi-Interact system provides information about the risk of Drug-Drug and Drug-CAM interactions, and pharmacokinetic and pharmacodynamic effects and mechanisms of interactions. The software identified and classified interactions according to their clinical relevance into the following categories: A, no known interaction; B, no action needed; C, monitor therapy; D, consider therapy modification; and X, avoid combination. The results were expanded through the present data storage of National Center for Complementary and Integrative Health (NCCIH),<sup>21</sup> PubMed, MEDLINE, Cochrane Library, and Memorial Sloan Kettering Cancer Center (MSKCC).<sup>22</sup> The scientific and English common names of the identified herbs were used to carry out a Medical subject heading (MeSH) search in the 3 electronic databases (PubMed, MEDLINE, and Cochrane Library on Wiley InterScience). Search terms were also constructed using the following keywords: herb-drug interactions, supplement interactions, adverse events, oncology. No restrictions on language or time of publication were declared. Additional references were also sought through hand searching the bibliographies of relevant articles. All studies that reported CDIs with breast-/gynecology-specific conventional systemic therapy were included. Studies reporting the general influences of BB-CAM on the pharmacological processes of conventional anticancer drugs were also included. Abstracts of reviews and original reports were studied, and those that met the inclusion criteria were evaluated by the authors. The research was done in the time period from September to November 2017. For details of the research refer to Supplementary File 2.

Additionally, the databases developed by the NCCIH and MSKCC to check for potential interactions with herbal supplements were screened. Every individual patient profile was assessed to determine the need of an

**Table 1.** Selected Patient, Illness, and Therapy Characteristics of the Study Cohort.

Characteristics	All Patients	
	Total Number, 448	Percentage of All Patients (n = 448), 100%
Age in years (mean ± SD)	62.2 ± 12.4	
Disease		
Breast cancer	361	80.6%
Early stage	147	32.8%
Advanced	201	44.9%
Recurrence	13	2.9%
Ovarian cancer	75	16.7%
FIGO I-3	23	5.1%
FIGO4	15	3.3%
Recurrence	37	8.3%
Other gynecological cancer	12	2.7%
Therapy line		
Breast cancer		
Neoadjuvant	70	15.6%
Adjuvant	89	19.9%
Metastasis first line	78	17.4%
Metastasis second line	50	11.2%
Metastasis third line	20	4.5%
Metastasis ≥ fourth line	53	11.8%
Recurrence first line	8	1.8%
Recurrence ≥ second line	5	1.1%
Ovarian cancer		
Neoadjuvant	1	0.2%
Adjuvant	37	8.3%
Recurrent	37	8.3%

intervention depending on the severity of the potential interaction discovered.

### Data Analysis

Descriptive statistics such as mean, SD, median, and absolute and relative frequencies were used to describe the distribution of potential CDIs as well as the patients' sociodemographic and disease- or treatment-related characteristics. Only completely filled-out questionnaires were analyzed. All analyses were conducted with IBM SPSS Statistics for Windows, Version 24 (IBM Corp, Armonk, NY). Statistical analysis was performed in cooperation with the Institute of Medical Informatics, Statistics and Epidemiology of the Technical University of Munich.

## Results

### Patient Characteristics

A total of 448 patients completed the questionnaire and were included in this study. The majority of the respondents (74.1%, n = 332) declared current BB-CAM use concomitant with systemic cancer therapy. Vitamin and mineral supplements (72.3%, n = 240), medicinal teas

(46.7%, n = 155), homeopathy (34.0%, n = 113), phytotherapy (30.1%, n = 100), and mistletoe (25.3%, n = 85) were frequently used. A total of 45.8% (n = 205) of the participants used various combinations of more than 1 BB-CAM method. An overview of the participants' systemic cancer therapy and their BB-CAM use is shown in Table 2. For reasons of better comprehension, systemic anticancer therapies are summarized into different classes, without displaying interaction profiles, in Table 2. Interactions assessment was done with respect to every specific herb-drug combination.

After separate analysis of the different time periods, no significant difference between the 2 time periods was detected. Especially the prevalence and use of specific BB-CAMs was compared (2014 vs 2017), and merely a slight difference in the prevalence of BB-CAM use was seen (71.5% vs 75.2%,  $P = 0.409$ ).

### Potential CDIs

After the first evaluation of the scientific literature, we decided to categorize the enormous number of different BB-CAMs patients were using. The 15 most common BB-CAMs reported that seem to play an important role in

**Table 2.** Patients' Conventional/Antineoplastic Systemic Therapy and BB-CAM Used.

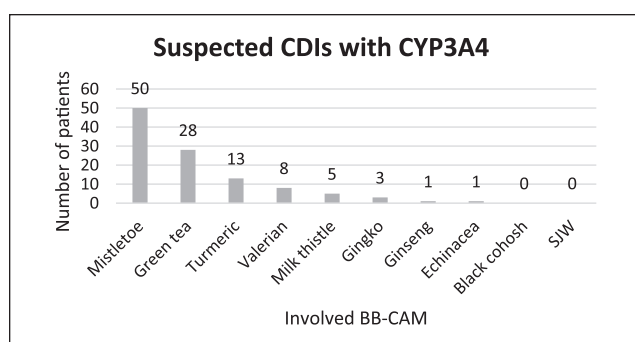
Conventional therapy	Total	Number of Patients Using BB-CAM															
		Mistletoe	Milk Thistle	St John's Wort	Gin-seng	Ginkgo	Echinacea	Turmeric	Black cohosh	Valerian	Antioxidants	Minerals	Homeopathy	Green Tea	Ginger Tea		
Chemotherapy	278																
Anthracycline	67	17	1	0	1	2	1	7	0	2	10	21	25	9	13		
Alkylating agent	46	14	1	0	1	2	1	6	0	2	8	14	20	5	12		
Antimetabolite	35	3	0	0	0	0	0	0	0	1	5	5	3	0	1		
Platinum derivative	51	12	3	0	0	0	0	1	0	1	13	17	16	5	6		
Taxane	108	27	3	0	0	1	0	5	0	2	25	33	32	14	17		
Vinca alkaloid	7	3	1	0	0	0	0	0	0	0	3	3	3	0	1		
Halichondrin B analog	9	5	2	0	0	0	0	3	0	0	2	4	6	3	3		
Other	9	0	0	0	0	0	0	0	0	0	3	4	0	3	3		
Target therapy	196																
Anti-HER2	92	20	2	0	0	3	0	2	0	3	21	35	27	15	11		
Angiogenesis inhibitor	69	10	3	1	0	0	0	3	0	4	13	20	20	5	6		
CDK4/6 inhibitor	35	5	2	0	1	0	2	2	0	1	12	10	7	4	6		
Immune modulator	2	0	0	0	0	0	0	0	0	0	0	1	0	1	0		
Others	67	13	3	1	1	1	0	1	1	1	12	18	16	7	5		
Endocrine	150																
Aromatase inhibitor	105	8	2	1	0	0	1	3	0	7	28	41	20	17	8		
Antiestrogen	51	7	2	2	1	0	1	1	1	0	6	13	8	4	4		
Bisphosphonates	129	15	2	2	0	0	1	5	0	5	24	38	26	16	12		

**Table 3.** Selected Pharmacokinetically Involved Substrates With Interactions Between Anticancer Drugs and Herbs.

Pharmacokinetically Involved Substrates	Anticancer Drug	Herb	
		Induction	Suppression
Cytochrome P450 (CYP) enzymes	CYP2A6	Cyclophosphamide	Ginseng <sup>a</sup>
	CYP2C9	Cyclophosphamide	Ginseng, <sup>a</sup> ginkgo, <sup>a</sup> milk thistle, <sup>a</sup> Echinacea <sup>a</sup>
	CYP2D6	Tamoxifen, doxorubicin	Black cohosh, <sup>a</sup> ginseng, <sup>a</sup> valerian, <sup>a</sup> ginkgo <sup>a</sup>
	CYP3A4	Cyclophosphamide, vinorelbine, paclitaxel, docetaxel, tamoxifen, anastrozole, doxorubicin	Echinacea, <sup>b</sup> black cohosh, <sup>a</sup> ginkgo, <sup>a</sup> ginseng, <sup>a</sup> green tea, <sup>a</sup> milk thistle, <sup>a</sup> mistletoe, <sup>a</sup> turmeric, <sup>a</sup> valerian <sup>a</sup>
Drug transporter	P-glycoprotein	Docetaxel, doxorubicin, paclitaxel, topotecan, tamoxifen, epirubicin	St John's wort <sup>b</sup> Milk thistle, <sup>a</sup> turmeric <sup>a</sup>

<sup>a</sup>Preclinical interaction, no effect in clinical trials.

<sup>b</sup>Preclinical and clinical interactions.



**Figure 1.** Distribution of CDIs with CYP3A4 sorted by highest number of patients with potential CDI.

Abbreviations: BB-CAM, biologically based complementary and alternative medication; CDI, CAM-drug interactions; SJW, St John's wort.

CDIs were the following: mistletoe, milk thistle, St John's wort (SJW), Panax ginseng, Ginkgo biloba, Echinaceae purpurea, turmeric, black cohosh, valerian, antioxidants (vitamins A, C, and E), minerals (selenium, zinc, magnesium), homoeopathy, green tea, and ginger tea. TCM methods were excluded from the interaction assessment because detailed information about the TCM method used was missing.

Analyzing individual CAM-drug combinations with the Lexicomp interaction database system did not reveal any harmful CDIs. Further research of the current literature showed that the main cause of CDIs is an increased risk for potential pharmacokinetic interactions. Table 3 illustrates potential pharmacokinetic interactions between anticancer drugs and herbs.<sup>17,18,23-32</sup>

In 82 patients (82/448, 18.3%), those CDIs were evaluated on a pharmacokinetic basis that were suspected to have interactions with the metabolism of cytochrome P450 (CYP) enzymes and most frequently of CYP3A4 (Figure 1).

In consequence, this means that 54% (82/153) of the patients using herbs as a complementary medication are

suspected to have CDIs. Here, the term *suspected CDIs* includes interactions that are predicted to cause effects based only on in vitro studies that have not been confirmed or have been refuted in human clinical trials.

The present analysis showed that 1 patient seemed to be in danger of a potential clinically relevant interaction of Echinacea and cyclophosphamide caused by a metabolism with CYP3A4. The other 81 patients were evaluated as "suspected CDIs" because interactions could not be verified in clinical trials. The interaction assessment within the mentioned sources could not detect any CDI with minerals and/or antioxidants.<sup>33</sup> Table 4 describe the interaction ratings in separate BB-CAM groups via the different assessment levels (Lexi-Interact, MSKCC, NCCIH, PubMed/MEDLINE/Cochrane Library) and clinical relevance through analysis of the medical record of the user.

Findings of the interaction assessment did not result in the necessity of treatment with respect to the CDIs. Not a single patient reported a remarkable negative effect of BB-CAM use.

## Discussion

The findings show a frequent and ongoing reported use of BB-CAM during systemic cancer therapy in patients with breast and gynecological cancer (74.1%). In all, 81 (18.1%) participants showed characteristics that led to a classification of "suspected CDIs." Only 1 patient seemed to be in danger of a potential clinically relevant interaction.

According to the literature, this is an overall high number of BB-CAM use.<sup>10,11,17,34</sup> Herbs are the most popular form of BB-CAM with the greatest potential to cause harm and undertreatment as a result of interactions with conventional anticancer drugs (herb-drug interactions). To our knowledge, only a few reports have studied CDIs specifically. Furthermore, hardly any data have been published reporting a number of patients in danger of interactions

**Table 4.** Interaction Rating of Specific BB-CAMs via the Different Assessment Levels and Clinical Relevance.

BB-CAM Method	Interactions via				
	User	Suspected CDI		Potential Clinical CDI	Clinically Relevant CDI
	By Questionnaire	Lexi-Interact	MSKCC/NCCIH	NCCIH/PubMed/MEDLINE/Cochrane Library	Medical Record of User
	No. of Patients (Percentage of BB-CAM Users, n = 332)	No. of Patients	No. of Patients (Percentage of Method Users)	No. of Patients	No. of Patients
Interaction rating of mistletoe via the different assessment levels and clinical relevance					
Mistletoe	85 (25.6%)	0	50 (58.8%)	0	0
Interaction rating of Phytotherapy via the different assessment levels and clinical relevance					
Milk thistle	13 (3.9%)	0	5 (38.5%)	0	0
St John's wort	4 (1.2%)	0	0	0	0
Ginseng	2 (0.6%)	0	1 (50.0%)	0	0
Gingko	5 (1.5%)	0	3 (60.0%)	0	0
Echinacea	3 (0.9%)	0	1 (33.3%)	1	0
Turmeric	25 (7.5%)	0	13 (52.0%)	0	0
Black cohosh	1 (0.3%)	0	0	0	0
Valerian	15 (4.5%)	0	8 (53.3%)	0	0
Interaction rating of medical teas via the different assessment levels and clinical relevance					
Green tea	58 (17.5%)	0	28 (48.3%)	0	0
Ginger tea	59 (17.8%)	0	0	0	0

caused by BB-CAMs that are based on the analysis of individual medication data.<sup>17,18,35</sup> One systematic research study published by Zeller et al<sup>17</sup> showed a similar design compared with the present study but with a different result for the number of CDIs. Zeller et al reported that “three quarters of users of substance-bound CAM are at risk of interactions.”<sup>17(p. 360)</sup> Previous studies have shown enormous differences in the number of interactions between CAM and anticancer treatment. The number of patients with potential CDIs ranges from 27% up to 90% of the participants.<sup>16-18</sup>

The CDI assessment of this study examined the actual combinations taken by each patient. Furthermore, 81 patients (18.1%) were classified as having “suspected CDIs” because the interactions of a combination of BB-CAMs and CYP3A4-metabolized anticancer drugs were found in preclinical studies but not verified with clinical data. For the patients using BB-CAM substances, this number was 24.4%, and only 1 patient was in potential danger of a clinically relevant CDI. These numbers are independent of the received systemic cancer therapy. None of the patients reported any negative side effects of their combination of BB-CAM and systemic cancer therapy. In comparison to this study, prior research reported a high rate of clinically significant CDIs because they assumed an interaction even with low-level evidence that reported no clinically significant effect. Additionally, it can be assumed that existing clinical evidence that reported this missing clinically significant effect—for example, the study by

Schink and Dehus<sup>28</sup> about the effect of mistletoe on CYP450—was overlooked and was, therefore, not included in previous studies on the topic of CDIs. In consequence, these publications registered a greatly higher rate of CDIs.<sup>17,18,35</sup>

In the assessment of this study, all interactions found seemed to be caused by pharmacokinetic factors. Most potential pharmacokinetic interactions are generated by changes in the functionality or expression of CYP enzymes. Potential pharmacokinetic CDIs can include inhibition or induction of CYP450 enzymes, drug transporters like P-glycoprotein, and other enzymes or proteins. Of these enzymes, CYP3A4 is the most important CYP enzyme because approximately 70% of all drugs are substrates for it. BB-CAMs seem to have various influences on the metabolism of conventional drugs. This may lead to subtherapeutic drug levels in the body as well as to prolonged activity and even toxicity of a drug.<sup>23</sup>

Preclinical studies are essential to determine possible CDIs, but clinical trials have to prove whether these results are of clinical relevance to human health or not. For instance, preclinical data followed by clinical studies verified the danger of the well-documented pharmacokinetic interaction between SJW and drugs metabolized by CYP3A4.<sup>36</sup> However, clinical trials often seem to fail to confirm preclinical approved CDIs.<sup>23</sup> Of the 15 selected BB-CAMs in the present study, clinical data exist for various BB-CAM methods,<sup>23-25,27,29,31,32</sup> but clinical data predicting CDIs have only been documented for Echinacea and SJW.<sup>37,38</sup> There are

various reasons for the discrepancies between preclinical and clinical trials. Sprouse and van Breemen<sup>23</sup> provided a critical overview of the laboratory standards for testing the safety of BB-CAMs.<sup>23</sup> These results should be recognized and implemented to provide the required clinical evidence. Taking into account these difficulties with critical data collection and reliable interaction assessment, only 1 of the 82 identified potential CDIs in the present study seemed to be of clinical significance.

This potential clinically significant CDI is the result of a combination of self-medicated Echinacea and cyclophosphamide in a recurrence first-line therapy setting. The patient used *Echinacea purpurea* twice a day for a total daily dose of 1600 mg.

A recent review of the majority of preclinical studies on the pharmacokinetic effect of Echinacea concluded that it exhibits at least mild to moderate inhibition of CYP3A4 in most of the model systems tested.<sup>39</sup> This conclusion is strengthened by a recent animal study, in which standardized Echinacea extracts reduced rat CYP3A mRNA.<sup>40</sup> These results were proven in very few prospective clinical studies in humans. Even the few clinical studies reported, in particular, contradictory results. In summary, the clinical examinations suggest that Echinacea may have mild inductive effects on human CYP3A4 in vivo.<sup>37,41,42</sup> An induction of CYP3A4 could have a wide range of effects on anticancer treatment. In this specific case, the induction of CYP3A4 can increase the metabolism of the prodrug cyclophosphamide, even if CYP2B6 is more important for activation of cyclophosphamide. Thus, Echinacea, as an inducer of CYP3A4, may cause an increased level of active cyclophosphamide up to a toxic effect. Furthermore, the function of CYP3A4 lies mostly in the detoxification of cyclophosphamide. So Echinacea also increases the detoxification and, therefore, lowers the toxic effect of cyclophosphamide, which can lead at worst to a reduced plasma concentration and a decrease of the important antineoplastic effect. The recommended daily dose varies between manufacturers and for different administration forms. In previous clinical studies, a mild to moderate inductive effect of Echinacea with an intake of a total of 1600 mg/d for 8 to 28 days has been reported.<sup>43</sup> But according to Gurley et al,<sup>44</sup> even this effect might be unlikely. In the systematic review of 2012, they reported that “any clinically important drug interactions with Echinacea seem remote.”<sup>44</sup>

The majority of the “suspected CDIs” were caused by an interaction of mistletoe and anticancer therapy. The publications found were mostly in a preclinical setting.<sup>28,45,46</sup> Collectively, former studies reported no or minor induction and inhibition on CYP3A4 of mistletoe in preclinical studies. All mentioned studies agree on the thesis that a clinically significant effect of mistletoe on CYP3A4 seems unlikely.

Although this study detected just a few patients with potential suspected CDIs because of the use of valerian, ginseng, ginkgo, and green tea, Sprouse and van Breemen<sup>23</sup> reported impressively the problem of actual data on herb-drug-interactions, or as Gurley et al<sup>44</sup> said, “in vitro predictions and in vivo realities.” (p. 1484) The majority of these BB-CAMs had been predicted to cause CDIs using preclinical assays, but clinical testing showed no effect. The large variability in the quality of reporting clinical data may be produced by the combination of the lack of standardization of herbal products, coupled with variable experimental design across laboratories.<sup>23</sup> Nevertheless, completely missing clinical data are a fundamental problem for an adequate interaction assessment, but missing clinical effect in existing publications should not be overlooked.

Within the scope of a correct assessment of the safety of CAM, there is furthermore an urgent need for critical and detailed data collection. CDI evaluation seems to be challenging because of the large number of components in one herb that may interact differently in various conditions, and herbal medicine is not subject to the same quality control as prescription drugs.<sup>31</sup> Thus, the content of the active ingredients may vary among manufacturers or product batches and could have different effects on the human body. Additionally, it is of great importance to register the detailed dosage of the BB-CAM taken. Previous studies showed a lack of information regarding patients' complementary medication. BB-CAM users in the present study largely took BB-CAMs in the recommended or lower doses, including homeopathic dosages. At a homeopathic dosage of D6, the dilution contains no molecules from the primary extract and, thus, no interactions are detectable. For instance, the used dosage of mistletoe in our study varied from 0.1 to 1 mg 1 to 3 times a week. No CDIs were seen at this dose.<sup>45</sup> To reveal CDIs in a clinical setting, correct collection of the dosage and frequency of BB-CAM medication is indispensable. Compared with other substances, a higher dosage is more likely to cause interactions. Therefore, interactions regarding BB-CAMs and systemic oncological therapy have been analyzed. Interactions between BB-CAMs and concomitant medications, for example, hypertensive medication, were not analyzed and will be the object of further research.

It is urgent to determine detailed information about the patients' use of BB-CAM, including data on manufacturer, dosage, and frequency. The critical and practical assessment of CDIs is only feasible when there are clinically implemented standards for herbal medicine. In contrast to former CDI assessments, our study registered the dosage and frequency of BB-CAM. Moreover, we analyzed patients' complementary medication in view of preclinical and clinical data and, thus, revealed patients in potential

danger of clinically relevant interactions of BB-CAM use concomitantly with systemic cancer therapy.

In spite of the widespread use of CAM, communication about CAM treatment is still missing between patients and health care providers.<sup>35</sup> However, it is essential to follow the SIO guideline about open discussions about CAM issues and critical CDI assessments to provide a consistent holistic therapy setting for cancer patients. To protect patients from inappropriate and even dangerous use of CAM, the integrative consultation program was established at our University Hospital Klinikum rechts der Isar in 2013 for gynecological and obstetric patients (ZIGG). Gynecologists, oncologists, and trained nurses<sup>22</sup> work in an interdisciplinary team to provide the optimal comprehensive care for patients. Special skills in phytotherapy, homeopathy, anthroposophical medicine and other CAM treatments contribute to the indispensable know-how of professionals working in such an integrative center.

These study results should be interpreted keeping in mind some limitations. First, we cannot exclude recall bias, because BB-CAM intake was based on self-report. Another limitation lies in the study cohort itself. Because a structured, integrative consultation program exists at the outpatient clinic, more patients are aware of integrative therapies and hence are possibly more likely to use BB-CAM. It would be interesting to know how the patients were influenced, on one hand, just because of the existence of a consultation service for CAM and, on the other hand, how the consultation service changed their behavior and compliance on CAM use. Further studies regarding these interesting questions are ongoing and part of future research in our clinic. Furthermore, much more available information is needed besides the actual cited databases to fill the gap of missing clinical evidence about the safety of BB-CAM in gynecological oncology.

## Conclusion

Our data demonstrated high overall use of BB-CAM by cancer patients undergoing systemic therapy. In comparison to other studies, potential interactions between BB-CAM and systemic cancer therapy were mostly unlikely and classified as “suspected CDI.” Only 1 patient was detected to be in danger of a potential clinically meaningful CDI.

Although the potential for drug-drug interactions must be investigated for all new drugs before being approved, CDIs remain underexplored. The increasing popularity of CAM, and especially BB-CAM, worldwide makes this issue particularly urgent.

## Authors' Note

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional

and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The final version of the questionnaire was approved by the Ethics Committee of the Technical University of Munich (TUM) with project number 412/14.

Participation in the study was voluntary. By filling out the questionnaire, the patients gave their consent to the survey and collection of personal data.

The author warrants that the work has not been published before in any form, that the work is not being concurrently submitted to and is not under consideration by another publisher, that the persons listed above are listed in the proper order, and that no author entitled to credit has been omitted. The article does not include information about an individual person.

Supporting data and material of this study are stored by the corresponding author at the Department of Gynecology and Obstetrics, University Hospital Klinikum rechts der Isar, Technical University of Munich and are available on request: please contact the corresponding author.

DP conceived of the presented idea, developed the theoretical formalism, and designed the study. LD carried out the study and the systematic research, performed the computations, and wrote the article with support from EK, M Kalder, and DP. M Kiechle and CB supervised the project. All authors discussed the results and contributed to the final article.

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## Declaration of Conflicting Interests

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