

2 Complementary and alternative therapeutic approaches in patients with early breast 3 cancer: a systematic review

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8

9 *Key words:* acupuncture, breast cancer, herbals, mistletoe, phytoestrogens, proteolytic enzymes, psychological
10 therapies, soy, trace elements, vitamins

11 Summary

12 Complementary and alternative medicine (CAM) is becoming increasingly popular, particularly among patients
13 with breast cancer. We have done a systematic review of studies published between 1995 and February 2005,
14 identified through a comprehensive search. CAM encompasses a wide range of treatment modalities, including
15 dietary and vitamin supplements, mind-body approaches, acupuncture, and herbal medicines. The objectives of
16 CAM treatments are diverse: reduction of therapy-associated toxicity, improvement of cancer-related symptoms,
17 fostering of the immune system and even direct anticancer effects. Clinical trials have generated few or no data on
18 the efficacy of CAM, whether regarding disease recurrence, survival, overall quality of life or safety. Some CAM
19 methods may even have adverse effects or reduce the efficacy of conventional treatment. The primary justification
20 for CAM is based on empirical evidence, case studies, and hypothetical physiological effects. We conclude
21 that available data on CAM modalities in the treatment of early-stage breast cancer does not support their
22 application.

23 Introduction

25 Every oncologist has been faced with questions from a
26 breast cancer patient such as “*What vitamins or minerals
27 should I be taking doctor? And how about mistletoe?*”
28 Depending on the attitude of individual doctors, the
29 answer will range from total rejection to complete
30 acceptance of any kind of complementary and alterna-
31 tive medicine (CAM). It might be helpful for clinical
32 oncologists to be aware of the available data regarding
33 the efficacy and safety of the most popular CAM
34 methods used by their patients. As shown in Figure 1
35 CAM does not inhibit the tumor growth.

36 CAM has been defined by the National Center for
37 CAM as a group of diverse medical and health care
38 systems, practices, and products that are not normally
39 considered to be conventional medicine [1,2]. These
40 treatments might be undertaken adjuvant to, or instead
41 of, conventional treatment. Complementary medicine is
42 extremely popular. In 1993, in a ground breaking study,
43 Eisenberg et al. [3] showed that patients paid approxi-
44 mately \$13.7 billion for these treatments, mostly out of
45 their own pocket. Recent studies have shown that 48–
46 98% of all breast cancer patients use some form of
47 CAM, [4,5] and that almost 50% of them never discuss
48 their use of CAM with their oncologist [6,7].

This article will review and evaluate the relevant lit- 49
erature between 1995 and March 2005 on the pros and 50
cons of CAM effectiveness for patients with early-stage 51
breast cancer. Data for review were identified by sear- 52
ches of following databases: a 53

Keywords included in the search strategy: 54
“breast cancer survivors” or “patients with breast 55
cancer” and 56

- safety or side effects 57
- Mistletoe 58
- Phytoestrogens 59
- Vitamins, 60
- Minerals, 61
- Trace elements, copper, selenium, zinc 62
- Enzymes 63
- Herbal medical products 64
- Acupuncture 65
- Psychological therapies/hypnosis 66

Search was limited to: Clinical trials, human, animal, 67
cell culture and English language. Case reports were 68
excluded. 69

Although many useful articles on unconventional 70
therapies appear in the lay literature, magazines and 71
books these articles were not considered . 72

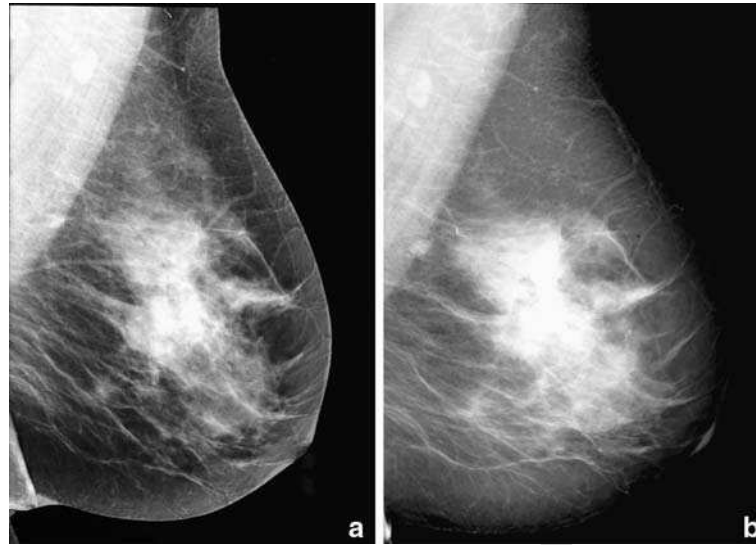


Figure 1. Mammograms of a 50 year old patient and histological proven breast cancer and tumor growth during CAM application: (a) before and (b) 6 months after own treatment with isopathic therapies and other approaches: Mucoracemosus fresenius, aspergillus niger, black cohosh, revitalization of gastroenteron by special diet and Chinese massage, electroacupunctur to splen, gaster, pancreas and pericard, alcalization of urine and twice daily pH control, complete tooth revitalization, reduction of psychologic stress, 12 h sleep per day, diet without any dairy products, pork, sweets or alcohol, megadosis of vitamin C infusions (45 g/week), Se, Zn, Mg, Mn, Cu, Coenzyme Q10, immunmodulation with utilin, latensin and recarcin.

Is the use of CAM for breast cancer supported by evidence-based medicine?

75 Decision-making in conventional medicine should ideally be based on biological mechanisms, clinical experience and statistical evidence. It treats by removing a presumed cause of sickness and success is measured by determining distinct treatment endpoints [8]. CAM methods tend to stimulate innate and individual healing forces, which are known by many names and appear in different facets. Many of these methods are based on a view of life that integrates physical as well as metaphysical aspects into one non-analytical and often semi-religious picture. In many cases of CAM there are even *in vitro* and *in vivo* data from animal models to support such hypotheses. Clinical data are rare and consist mainly of empirical work or case reports. Finally, data from primary prevention studies have been applied to patients who have already had early-stage breast cancer.

91 The US National Cancer Institute (NCI) [9] provides a detailed report on the “Level of Evidence for Human Studies of Cancer CAM”. So far, CAM methods for breast cancer survivors do not meet evidence-based medicine criteria [8]. Most studies are epidemiological multicentre retrolective cohort study, qualifying for LOE “3a”. Therefore we could not use the comprehensive search strategies described by Robinson and Dickersin [10].

Who uses CAM?

101 Factors favoring the use of CAM in cancer patients are quite diverse. In general, these patients are not

dissatisfied with conventional medicine, but find alternatives to be more congruent with their own beliefs and philosophical orientations towards health and life [11,12]. Patients gather information from various sources, including personal communication with friends and relatives, print media, television programs and the Internet. Archetypal patients who request and use CAM are usually well-informed, young, urban professionals with a higher income [13–16]. The heterogeneity of coverage practice for CAM is caused by different insurance policies, practitioner requirements and health plans within each carrier [17–19]. Own, unpublished data revealed that 45% of patients included in randomized studies used any kind of oral or parenteral applicable CAM (data prepared for publication).

118 There are marked cultural differences in the way that doctors, as well as patients, integrate CAM into treatment regimens. While only 4% of Norwegian doctors believe that CAM might have a role in the treatment of cancer patients, roughly 20% of German doctors do so [20,21]. In Europe, for example, preferred therapies include mistletoe extracts, vitamin therapies, selenium, and phytoestrogens, while in Asia traditional Chinese or Japanese medicine, spiritualism, hypnosis and aromatherapy enjoy widespread popularity. North American cancer patients are commonly treated using acupuncture, hypnosis and spiritualism, as well as vitamin therapies and extracts from various plants [22,23]. Special diets or mixtures such as “macrobiotica”, [24] “garlic” (*Allium sativum*), [25] “ginger” (*Zingiberaceae*), [26] and mixtures of nutrients, such as “Nitter therapy”, [27] “Gerson”, [28] “di Bella Multitherapy”, [29] and “Ukrain” [30] enjoy only local popularity.

Why do patients turn towards CAM?

137 Although expectations are quite individual, cancer
138 patients may have quite specific goals. By using CAM
139 they hope to achieve a strengthen of the immune system
140 (91%), a decrease in therapy-associated toxicity (61%),
141 assistance of conventional therapies (58%), a direct anti-
142 cancer effect (42%) and to alleviate cancer-derived
143 symptoms (34%) [31]. A correlation between any form
144 of CAM and disease-free or overall survival has not
145 been demonstrated yet.

146 Many cancer patients try to look for some sort of
147 reason to explain the onset of their disease, or they may
148 feel some sort of guilt regarding their illness. They often
149 come to the conclusion that they have led an "unhealthy
150 life" and that now might be the time to start to care for
151 their body in various ways. They might act to reduce
152 stress, and add vitamins, trace elements or other sub-
153 stances to their diet. Most of these substances are said to
154 "strengthen" the immune system. Another feature is a
155 fear of the side effects of conventional therapy. Finally,
156 some practitioners may find it easier to prescribe some
157 CAM agent, rather than facing the up to the dismal
158 outlook of incurable disease, and consequently CAM is
159 prescribed mainly by General Practitioners and other
160 non-specialized doctors, whereas oncologists tend to be
161 quite restrictive in recommending it to their patients [21].

Complementary and alternative medicines

163 Mistletoe

164 Mistletoe preparations are particularly popular in Eur-
165 ope. They are usually extracts from common mistletoe
166 plants that live in symbiosis with many European trees.
167 These extracts contain mistletoe lectines and viscotox-
168 ines, which have been shown to modify intracellular
169 protein synthesis, stimulate cytokine production, inhibit
170 tumor colonization and induce cell necrosis *in vitro*.
171 Simultaneous treatment of breast carcinoma cells
172 (MCF-7) with mistletoe lectines rendered them more
173 sensitive to the induction of apoptosis by TNF- α . Data
174 from mice models suggested an anti-cancerous, anti-
175 metastatic, pro-apoptotic and cytotoxic effect [32,33].
176 However, 84 non-randomized clinical trials have failed
177 to establish whether use of mistletoe preparations lead
178 to an increased overall survival. Many of the studies
179 examine the issue of improving quality of life
180 using mistletoe preparations, while undergoing conven-
181 tional chemotherapy [34,35]. A randomized, placebo-
182 controlled, double-blind, multicenter clinical trial
183 included 272 breast cancer patients receiving adjuvant
184 cyclophosphamide, methotrexate and 5-fluorouracil
185 (CMF) chemotherapy. In this study, the standardized
186 mistletoe extract lead to a significant improvement in
187 quality of life [36]. Furthermore, standardized mistletoe
188 extract was shown to significantly influence the immune
189 status of tumor patients [37].

In a recent meta-analysis, Kienle et al. report that
most of the 23 examined studies were based on very
poor quality data [38]. There are currently no placebo-
controlled double-blind randomized clinical trials that
prove the efficacy of mistletoe preparations in terms of
recurrence-free or overall survival after breast cancer
[39,40]. It seems to be extremely difficult to complete a
prospective placebo-controlled, double-blind mistletoe
trial in this setting: as Gerhard et al. [41] reported
recently, only 6% of suitable patients agree with ran-
domization.

There are also safety concerns regarding the use of
mistletoe preparations. *In vitro* studies have shown that
they enhance DNA repair mechanisms in peripheral
blood mononuclear cells. Induced cytokines may stim-
ulate tumor cells and influence apoptotic pathways in
healthy tissue [42,43]. Whether these *in vitro* data are
relevant to the human *in vivo* situation, in which mis-
tletoe preparations are usually given concomitantly with
conventional chemotherapy, remains an unresolved
question.

Phytoestrogens

Phytoestrogens are classified as water-soluble isoflav-
ones and lipophilic lignanes. Isoflavones are found
mainly in soya beans and lignanes in linseed wheat,
fruit, flaxseed and vegetables. Depending on their
metabolism and concentration, phytoestrogens exe-
cute antiestrogenic (2-hydroxyestron) or estrogenic
(16- α -hydroxyestron) effects. They block estrogen
receptors and lead to decreased activation of estrogen,
compared to physiologic estrogen effects in premeno-
pausal women. Furthermore, they have been shown to
stimulate the synthesis of sex hormone-binding globulin,
inactivate estrogen and to inhibit tyrosine kinase activ-
ity, aromatase activity and angiogenesis [1,44-47].
Phytoestrogens increased estrogen-responsive human
breast cancer cell proliferation at low doses, but para-
doxically caused profound inhibition of growth at
higher doses (Figure 2). There are currently six pub-
lished randomized controlled trials, only one of which
was able to show a positive effect in cancer patients [48].
A meta-analysis of 18 epidemiological studies on the
incidence of breast cancer was not able to show any
preventive effect of soya beans [49]. At present, there is
no evidence to support recommendations to use phy-
toestrogens, either to treat breast cancer nor to ease nor
to prevent climacteric symptoms [50-53].

Phytoestrogens, especially soya-derived products, are
extremely popular for treating postmenopausal symp-
toms in women with breast cancer while undergoing
tamoxifen therapy. The principal constituents of soy,
isoflavones genistein and daidzein, are structurally sim-
ilar to 17 β -estradiol and produce weak estrogenic effects
[54]. Genistein, has been shown to counteract the
inhibitory effect of tamoxifen on breast cancer growth
and increased expression of estrogen-responsive genes *in*
vitro [55,56]. Experimental data indicate that soya can

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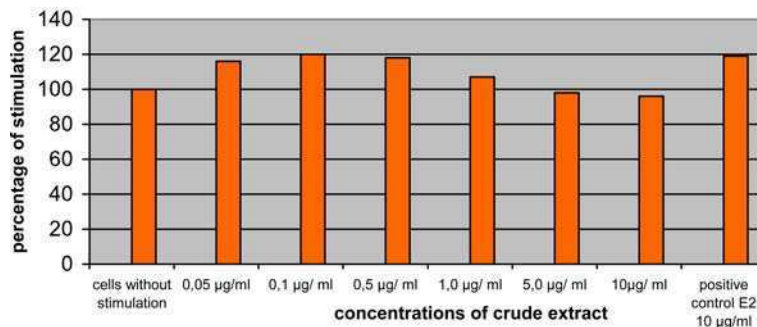
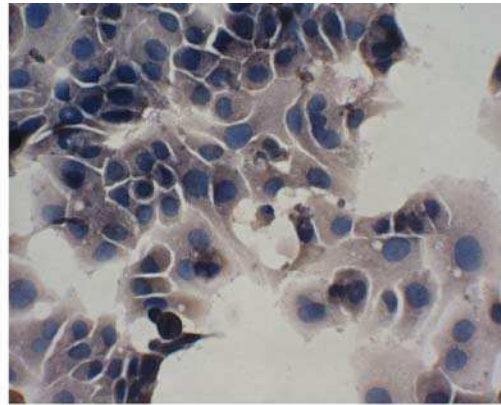


Figure 2. Influence of a flaxseed crude extract on the ER-positive breast cancer cell line MCF-7: higher concentrations of the flaxseed crude extract show an inhibitory effect, whereas lower concentrations provide stimulatory effects in comparison to 17β-Estradiol.

247 stimulate the growth of estrogen-dependent tumors in
 248 mice [57,58]. Recent findings suggest that oxidative
 249 DNA damage by isoflavone metabolites plays a role in
 250 tumor initiation. Isoflavones may increase cell prolifer-
 251 ation by estrogen receptor binding and induce tumor
 252 promotion and/or progression, leading to cancer in
 253 estrogen-sensitive organs [59]. Moreover, some phy-
 254 toestrogens, like *Trifolium pratense* (red clover), *Cimi-
 255 cifuga racemosa* (black cohosh), *Humulus lupulus* (hops),
 256 *Angelica sinensis* (dong quai), and *Glycyrrhiza glabra*
 257 (licorice), may exert their estrogenic influence through
 258 receptor-dependent and/or -independent mechanisms.
 259 These findings have led to speculation that phytoestrogens
 260 should not be given to patients with hormone-
 261 dependent cancers [60].

262 At present, it seems sensible to discourage the use of
 263 soya-derived products by patients with estrogen-depen-
 264 dent tumors (e.g., breast or endometrial cancer).

265 *Vitamins*

266 Vitamins A, B and E, as well as trace elements, like
 267 selenium, are known to capture free radicals. They have
 268 a role in preventing lipids from oxidizing, are involved in
 269 DNA-repair mechanisms and influence apoptotic path-
 270 ways [61–63]. An anti-cancer effect has been shown *in
 271 vitro*. To date, no studies have established a role for
 272 vitamins and selenium in the prevention of breast cancer
 273 [64]. In a randomized controlled trial, 2972 patients with
 274 invasive or non-invasive breast carcinoma received
 275 either 200 mg of the vitamin A preparation (Fenretinide)
 276 per day or no therapy [65]. After a median follow-up of

97 months, no significant differences in distant disease-
 free or overall survival could be demonstrated. This
 trial, however, was able to show a significant reduction
 in local breast cancer recurrence for premenopausal
 women (HR: 0.65; 95% CI: 0.46–0.92). Bexarotene, a
 retinoid X receptor-selective retinoid with preclinical
 antitumor activity in breast cancer, revealed only limited
 efficacy in 145 patients with refractory metastatic breast
 cancer [66].

A cohort study, examining high doses of vitamin
 preparations with beta-carotene, vitamin C, niacine,
 vitamin B3, selenium, coenzyme Q and zinc, started
 6 months after diagnosis in addition to standard ther-
 apy, showed a marginal negative effect after a median
 follow up of 68 months [67]. Another study established
 that above-normal serum concentrations of vitamin E
 had a negative effect on breast cancer patients [68].

In conclusion, there is no role for supplementation of
 vitamins or trace elements in breast cancer patients,
 providing they adopt a balanced and healthy diet [69].
 The only exception to this rule seems to be patients
 suffering from a concomitant illness leading to malab-
 sorption or maldigestion. For example, patients, who
 develop mucositis with chemotherapy may be supple-
 mented with the recommended daily allowance of vita-
 mins, minerals and trace elements [70].

Trace elements

Selenium is known to enhance the number of natural
 killer cells and interferon-γ-secretion *in vitro*. Preventive
 effects have also been demonstrated in patients with

307	prostate and gastric cancer, but not breast cancer	symptoms of the disease and the side effects of adjuvant	364
308	[64,71,72]. Selenium is an integral part of the tertiary	antineoplastic therapies [84].	365
309	structure of many enzymes (e.g. superoxidismutase,		
310	catalase, glutathionperoxidase) that are known to safe-	<i>Herbal medical products</i>	366
311	guard cells against oxidation by free radicals. In our		
312	daily diet, selenium is found mostly in broccoli, leek and	Numerous herbal medical products are promoted as	367
313	red meat, and a single Brazil nut per day provides	CAM. <i>In vitro</i> studies of individual components or	368
314	enough selenium to meet the regular daily uptake. It	mixtures have shown some biological activity, com-	369
315	may also provide between chemotherapeutic agents,	prising antioxidant, endocrine, immunostimulant and	370
316	such as doxorubicin or paclitaxel, and selenium has been	antitumor properties. Preparations of plants, based on	371
317	shown in studies with breast cancer cell-lines [73].	ancient recipes from Chinese or Japanese medical tra-	372
318	Among other mutations, tumor cells are known to show	dition, are mainly popular in Asia and North America	373
319	exceptionally high expression of antioxidizing enzymes.	[85]. Many mixtures are known to have an anticancer-	374
320	As selenium is needed by many of these enzymes in	ous effect <i>in vitro</i> [86–88], yet, no clinical trials have been	375
321	order for them to function, it may well be possible that	performed to study efficacy and safety in breast cancer	376
322	selenium reduces the susceptibility of cancer cells to	patients.	377
323	chemotherapy rather than protecting healthy tissue.	Although at first sight, herbal remedies appear safer	378
324	Alterations in serum concentrations of selenium in wo-	and “more natural” than conventional drugs, significant	379
325	men with breast cancer appear to be a result, rather than	adverse effects and drug interactions may still need to be	380
326	a cause of cancer [72].	considered. Many herbs exert an anticoagulatory effect	381
327	Copper and zinc also form part of many enzyme	via induction of cytochrome P450 pathways [89], Kava	382
328	complexes known to protect against free radicals	and comfrey are known to be hepatotoxic. Safrol, one of	383
329	[74–76]. The frequency of distant metastasis was shown	the ingredients of “Dong Quai” has been shown to be	384
330	to be significantly higher in 182 breast cancer patients	tumorigenic, while many herbs, including <i>Aristolochia</i>	385
331	with decreased serum copper levels [77]. In another	<i>fangchi</i> , are potentially nephrotoxic and have been	386
332	study, however, <i>N</i> -methyl- <i>N</i> -nitrosurea-induced breast	shown to cause acute interstitial nephritis and carci-	387
333	carcinoma tissue of the rat was shown to accumulate	noma of the transitory epithelium [1,70]. A complete	388
334	zinc to a significantly higher degree than surrounding	review of herbal remedies and their potential adverse	389
335	tissue. This suggests a potential role for zinc in tumor	effects has recently been published by Sparreboom et al.	390
336	genesis [78].	[23].	391
337	Changes in serum levels of trace elements may gener-	Green tea is said to prevent cancer because of its	392
338	ally be the result rather than the cause of breast can-	antioxidating ingredients as well as its cytotoxic	393
339	cer, while tumor cells have an increased requirement for	polyphenols. However, in a current meta-analysis of	394
340	trace elements. There are few clinical data to support the	studies comparing the daily intake of 1 versus 5 cups of	395
341	use of selenium, zinc or copper supplementation in the	green tea with respect to the risk of developing breast	396
342	prevention or treatment of breast cancer and, so far, no	cancer, no correlation (relative risk: 0.84, 95% CI: 0.57,	397
343	randomized clinical trials have demonstrated improved	1.24, $p=0.69$) could be established [90]. Breast cancer	398
344	quality of life or prolonged overall survival using trace	patients consuming more than 5 cups per day were seen	399
345	element supplementation [15,79].	to have a prolonged recurrence-free and overall survival	400
346	<i>Enzymes</i>	[91]. Other data, involving patients with prostate cancer,	401
347	The popularity of enzyme preparations has decreased	revealed a significant increase in the frequency of diar-	402
348	markedly since the advent of bovine spongiform	rhea and vomiting while showing no benefit with regard	403
349	encephalopathy (BSE) some years ago. One of the most-	to the malignant disease [92]. It should also be noted	404
350	studied enzymes, with respect to its presumed anticancer	that various additives are used to alter the taste or tol-	405
351	effect, is coenzyme Q10 (synonyms: <i>Q10</i> , <i>Co Q10</i> , <i>vita-</i>	erability of tea are sometimes seen to have other side	406
352	<i>min Q10</i>), which is synthesized by human cells as an	effects [26].	407
353	anti-oxidizing agent. Since it was shown to have an	Isopathic therapies is a system of healing using iso-	408
354	antiproliferating effect <i>in vitro</i> , <i>Q10</i> has been studied as	pathic/homeopathic medicines that assist in restoring	409
355	a cytostatic agent in the adjuvant setting [80], as well as	balance and harmony to an organism. The main objec-	410
356	a protective agent during chemotherapy [81]. Case	tive is to stabilize the pHs and slowly bring the fungus/	411
357	reports describing instances of complete remission while	mold back to a normal symbiotic state by using the	412
358	using Q10 [82] have never been backed up by clinical	isopathic remedies.	413
359	trials and in fact Q10 has even been shown to decrease	<i>Acupuncture</i>	414
360	the efficacy of radiotherapy in an animal model [83]. An		
361	epidemiological retrolective cohort analysis provides	Very few asymptomatic breast cancer survivors use	415
362	evidence that oral enzymes in breast cancer patients	acupuncture [4]. Acupuncture has been studied in breast	416
363	improves the quality of life by reducing signs and	cancer patients primarily with the intention of reducing	417

418 chemotherapy-induced nausea and vomiting, meno-
 419 pausal symptoms and pain perception [4,93,94]. An
 420 increasing body of data supports the efficacy of acu-
 421 puncture for cancer-related pain [95] and reducing the
 422 frequency of vomiting [96]. This effects, however, were
 423 of limited duration.

424 *Psychological therapies/hypnosis*

425 Many patients with cancer turn to psychological thera-
 426 pies like praying, spirit medicine, hypnosis, meditation,
 427 affirmation, imagery or rituals. Many studies have
 428 demonstrated interactions between the central nervous
 429 and the immune systems. While a negative effect of
 430 stress on immune responses has been demonstrated,
 431 there have also been published reports that psychologi-
 432 cal treatments can positively alter the immune system
 433 [97–99].

Is CAM safe?

435 While many forms of CAM are associated with mini-
 436 mal or no risk, this is not true for all such therapies.
 437 On the contrary, the combined use of CAM with
 438 certain anticancer drugs may increase or reduce the
 439 effects of either component [23,100]. Obviously, syn-
 440 ergistic therapeutic effects may complicate the dosing
 441 regimen of long-term medications or lead to undesired
 442 toxicities. Herbal preparations may interact with en-
 443 zymes and transport proteins in charge of drug
 444 metabolism. Although interactions are most likely to
 445 arise secondary to altered pharmacokinetics of the in-
 446 volved drugs [101], pharmacodynamic interactions
 447 [102] and the intrinsic toxicity of several herbs have
 448 also been documented. Aristolochic acids, for example,
 449 which are present in the Chinese herb *Aristolochia*
 450 *fangchi* may undergo a chemical reduction by hepatic
 451 cytochrome P450 (CYP1A1/2) or peroxidases in
 452 extrahepatic tissues to form reactive cyclic nitrenium
 453 ions. The latter has been found to be capable of
 454 reacting with DNA and proteins, potentially resulting
 455 in activation of H-ras oncogene, gene mutations and
 456 finally carcinogenesis [103]. When herbal preparations
 457 are taken by patients currently on chemotherapy,
 458 uncontrolled induction of various enzymes and trans-
 459 porters may also take place in tumor cells, subse-
 460 quently resulting in resistance to anthracyclines,
 461 epipodophyllotoxins, cisplatin, taxanes, and vinca
 462 alkaloids [104,105]. Likewise, catalytic inhibition of
 463 topoisomerase II_α in tumor cells by some herbs [106]
 464 might diminish the therapeutic response to anthracy-
 465 clines, dactinomycin, and etoposide [107]. Phytoestro-
 466 gens may also counteract the inhibitory effect of
 467 tamoxifen on breast cancer growth [55,59]. Otherwise
 468 black cohosh extracts increased the cytotoxicity of
 469 doxorubicin and docetaxel in cell culture [104]. Finally,
 470 there are also serious safety concerns about mistletoe
 471 applications [42,43].

A Norwegian longitudinal study, following 515 pa- 472
 tients with different cancer types for a median of 8 years, 473
 suggests that use of several types of specific alternative 474
 medicine may be associated with shorter survival (79% 475
 versus 65%). In a Cox regression model adjusted for 476
 demographic, disease and treatment factors, the hazard 477
 ratio of death for any use of CAM compared with no 478
 use was 1.30, (95% CI: 0.99–1.70; *p* = 0.056), suggesting 479
 that CAM use may predict a shorter survival [27,108]. 480

Conclusion: so, what should oncologists advise?

Oncologists should be aware of CAM approaches pre- 482
 valent in their patient population, should inquire about 483
 their use and should be able to counsel for or against 484
 them. There is no compelling evidence that any of the 485
 numerous complementary treatments available is suffi- 486
 ciently effective in breast cancer patients to justify its use 487
 (Table 1). It should be the responsibility of those who 488
 claim efficacy for CAM to support these claims with 489
 acceptable evidence, rather than the responsibility of 490
 those who criticize CAM to prove its non-efficacy. On 491
 the one hand, if more convincing data existed, there 492
 might be far less room for disagreement. On the other 493
 hand, if the medical profession rejects CAM because it is 494
 not evidence based this could be counter productive, as 495
 medical therapy is not merely concerned with evidence. 496
 The patient–doctor relationship and an individual’s 497
 beliefs concerning health and life are equally important. 498
 Empathic and supportive communication with the 499
 patient about complementary forms of treatment may 500
 well strengthen the patient–doctor relationship. Doctors 501
 should ask patients about their use of CAM and should 502
 talk openly and objectively about the evidence, or lack 503
 of it, for alternative or complementary cancer therapies. 504
 Discussions might include the fact that some forms of 505
 CAM are potentially linked with considerable risks, and 506
 that some are associated with neither prolongation of 507
 life nor improved quality of life. A particularly poorly 508
 documented aspect of CAM is its potential interaction 509
 with other medical agents or cancer treatments. 510

The concept of *evidence*, however, is a mainstay of 511
 conventional medicine to which these therapeutic 512
 approaches are proud to be an alternative to. Never- 513
 theless, in the U.S. the National Institutes of Health 514
 (NIH) Center for CAM [1] and the NCI are supporting 515
 well-designed studies of alternative medicine. Informa- 516
 tion on CAM is available through the NCI website and 517
 a field group within the Cochrane Collaborative. Com- 518
 plementary and alternative approaches may supplement 519
 conventional medicine in a helpful and meaningful way 520
 in future, and may increase patients’ approval of con- 521
 ventional treatment. However, the level of evidence for 522
 the benefits of CAM remains to be improved (Table 2). 523
 The authors cannot give any recommendations for 524
 breast cancer patients, because there are no data com- 525
 paring regular adjuvant treatment with any CAM 526
 treatment. 527

Table 1. Proven effects of different CAM approaches in breast cancer

Approach	Effects	<i>In vitro</i> data	Animal model	Randomized trial available	Recent references
Mistletoe	Preventive effect on breast cancer incidence			-	No data
	Anti-cancerous/-metastatic, pro-apoptotic, cytotoxic	+	+		[32,33]
	Immunomodulation		+		[37]
	Improved quality of life during systemic treatment			+	[35,36]
	Improved disease free survival				No data
Phytoestrogens	Preventive effect on breast cancer incidence	-	-	-	[48,49,59]
	Block estrogen activity in premenopause	+/-	-	-	[57,109-111]
	Abrogates tamoxifen effects		+		[56]
	Improved quality of life during systemic treatment/treatment of climacteric symptoms			-	[52,53,112]
Vitamins	Improved disease free survival				No data
	Preventive effect on breast cancer incidence			-	[64]
	Anti-cancer/-metastatic, pro-apoptotic	+	+		[61-63,113]
Antioxidants/trace elements	Improved quality of life during systemic treatment				No data
	Improved disease free survival			-	[65]
	Preventive effect on breast cancer incidence			-	[64,71,72]
	Anti-cancer/-metastatic, pro-apoptotic, antiangiogenic	+	+		[74-76,114]
Proteolytic enzymes	Improved quality of life during systemic treatment				No data
	Improved disease free survival				No data
	Preventive effect on breast cancer incidence				No data
	Anti-cancer/-metastatic, pro-apoptotic, antiangiogenic	+	+		[114]
Herbal medical products	Improved quality of life during systemic treatment				No data
	Improved disease free survival				No data
	Preventive effect on breast cancer incidence				No data
	Anti-cancer/-metastatic, pro-apoptotic, antiangiogenic	+	+		[86-88]
Acupuncture	Improved quality of life during systemic treatment				No data
	Alter the response to agents commonly used to treat breast cancer	+			[104-107]
	Improved disease free survival				No data
	Preventive effect on breast cancer incidence			+	[96]
Psychological therapies/hypnosis	Anti-cancer/-metastatic, pro-apoptotic, antiangiogenic				No data
	Improved quality of life during systemic treatment				No data
	Improved disease free survival				No data
	Preventive effect on breast cancer incidence immunomodulation			+	[99]
	Improved quality of life during systemic treatment			+	[98]
	Improved disease free survival			-	[115]

+ : Beneficial effect, - : Negative effect.

Table 2. Complementary treatment (tertiary prophylaxis) after breast cancer treatment with respect to improvement of disease free or overall survival. Level of evidence (LOE) and grade of recommendation (GR) according to the Oxford criteria [8] and the German Associations of Gynecologic Oncologist (AGO) "breast cancer" [116]

	Oxford level of evidence		Grade of recommendation	
	Disease free survival/ Overall survival	Quality of Life	Oxford	AGO*
Mistletoe	5	4	D	-
Soy/phytoestrogens	5	4	D	-
Vitamins	5	4	D	-
Trace elements (selen, zinc...)	5	4	D	-
Proteolytic enzymes (coenzyme Q10, papain, trypsin, chymotrypsin)	5	4	D	-
Herbal medical products	5	5	D	-
Acupuncture	5	3b	C	+/-
Psychological therapies/hypnosis	5	2c b	B	+/-

*AGO: grade of recommendation

++: This investigation or therapeutic intervention is highly beneficial for patients, can be recommended without restriction, and should be performed.

+: This investigation or therapeutic intervention is of limited benefit for patients and can be performed.

+/-: This investigation or therapeutic intervention has not shown benefit for patients and may be performed only in individual cases. According to current knowledge a general recommendation cannot be given.

-: This investigation or therapeutic intervention can be of disadvantage for patients and might not be performed.

---: This investigation or therapeutic intervention is of clear disadvantage for patients and should be avoided or omitted in any case.

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