Published in final edited form as:
Ann Pharmacother. 2007 October ; 41(10): 1617–1624. doi:10.1345/aph.1K221.

Potential Interactions between Complementary/Alternative Products and Conventional Medicines in a Medicare Population

Gary W Elmer, PhD,
Professor Emeritus, Department of Medicinal Chemistry, University of Washington

William E. Lafferty, MD,
Professor, Department of Health Services, University of Washington, billlaf@u.washington.edu

Patrick T. Tyree, AA, and
Research Consultant, Department of Health Services, University of Washington

Bonnie K. Lind, PhD
Assistant Research Professor, Department of Nursing, Boise State University

Abstract

Background—Despite the high prevalence of Complementary and Alternative Medicine (CAM) product use among the elderly, little is known about the extent of concurrent CAM-conventional medicine use and the potential for adverse reactions.

Objectives—To determine the prevalence of CAM product use concurrent with conventional medications, prescription and non-prescription, in a Medicare population and to assess the risk for adverse interactions.

Methods—Retrospective analysis was performed on Cardiovascular Health Study interview data from 1994, 1995, 1997, and 1999. The prevalence of concurrent combinations of CAM products and conventional drugs was tabulated. The adverse interaction risk was categorized as unknown, theoretical, and significant.

Results—Of 5,052 participants the median age was 75; 60.2% were female; 16.6% African-American; and 83.4% white. The percent using CAM products during the four time periods was 6.3, 6.7, 12.8 and 15.1. The percent using both CAM products and conventional drugs was 6.0, 6.2, 11.7 and 14.4. Of these, 294 individuals (5.8%) took combinations considered to have a significant risk for an adverse interaction. Combinations with risk were observed on 393 separate interviews. Most (379) involved a risk of bleeding due to use of ginkgo, garlic or ginseng together with aspirin, warfarin, ticlopidine or pentoxifylline. An additional 786 observations of combinations were considered to have some, albeit theoretical or uncertain, risk for an adverse interaction.

Conclusion—Concurrent use of CAM products and conventional medicines in a Medicare population was common. Research to define the risks of combining ginkgo and garlic supplements with aspirin should be of high priority.

Keywords

Interactions; herbal; elderly; garlic; ginkgo; ginseng; St. John’s wort

Correspondence to: William E. Lafferty.

INTRODUCTION

The use of complementary and alternative medicine (CAM) products remains prevalent in the U.S. population. The Slone survey[1] (random survey of the US population) found about half of those surveyed (n=2,590) took a prescription drug in the previous week and 16% of these prescription drug users also took one or more CAM supplements during the survey week. Among those over 65, the Slone Survey also showed that 23% of women and 12% of men had used five or more medications in the previous week. Of these, 14% had used herbal treatments in addition to prescriptions, supplements, and other over-the-counter drugs during the survey week. Despite the high prevalence of use of CAM products, little is known about the extent of specific CAM-conventional medicine concurrent use or the potential for adverse reactions from these combinations. The elderly are of special concern because polypharmacy is well documented, sensitivity to some medications is greater, and the organs that process many medications become less functional as people age. These factors raise the likelihood that potentially toxic drug combinations will occur. Of further concern is that it is generally recognized that about half of herbal product users do not discuss use with a healthcare professional creating a theoretically significant risk for adverse CAM product-drug interactions.

In this study, we reviewed the literature to assess the risk of combining various CAM medications with conventional medications. We determined the prevalence of the most common CAM product and conventional medication combinations and identified those that have the potential for adverse interactions.

METHODS

The study, “Race and Herbal Medications Among Medicare Recipients” (RHM), was approved by the University of Washington’s Institutional Review Board. Research involved analysis of secondary data originally collected as part of the Cardiovascular Health Study (CHS). CHS was a 10 year prospective population-based cohort study of risk factors for coronary heart disease and stroke in adults 65 years and older. The study and participating sites have been previously described.[2]

At each annual clinic examination and interview, CHS participants were asked to bring all prescription medications taken in the previous two weeks. Participants provided the interviewers with the medication containers. The interviewer transcribed from the label the drug name, strength, and dosing instructions. After the transcription process, the interviewer inquired how often the medication had been taken during the previous two weeks. Direct questions about the use of aspirin were also asked at each examination. Psaty describes these methods in detail.[3]

Five years into the CHS project, data collection was expanded to include non-prescription medications. Participants were asked to bring their non-prescription as well as their prescription medications to the clinic examination for interviewer transcription. Unlike the protocol for prescription medications, dosing information was not collected for non-prescriptions. For RHM summary analyses we categorized non-prescription medications into CAM products, vitamins, minerals, or other OTC. CAM products were defined as herbal (botanical) products or non-botanical dietary supplements (e.g., glucosamine) excluding vitamins and minerals. A small fraction (0.16%) of the non-prescriptions could not be characterized.

The RHM analysis used the medication data from four CHS annual examinations: (1) the fourth follow-up examination (1993–1994, the first year that non- prescription drugs were included in the examination); (2) the fifth follow-up examination (1994–1995); (3) the seventh follow-up examination (1996–1997); and (4) the ninth follow-up examination (1998–1999). Nearly

all CHS participants are either white or African-American. The 39 (0.8%) participants of other races were excluded from this analysis in order to allow for comparisons by race.

The dataset was prepared by listing the use of CAM products with all prescription medications and specific OTC medications. Tables produced from these data were manually reviewed for potential harmful interactions, based on the published literature, by a one of the authors (GWE) with research experience in the area of CAM product-drug interactions. Only CAM/prescription, analgesic, or cold medication product combinations used by two or more participants were considered. Assessment of interaction risk was based on a systematic review of the primary literature, recent reviews, four monographic databases,[4–6] one of which4 is updated "daily", and our own work. A literature search for reported adverse interactions for each CAM product that was used concurrently with a conventional medicine was conducted. Assignment of risk was a qualitative one based primarily on *in vivo* studies in humans or case reports. Risks of combinations were qualitatively assigned as follows:

None or information lacking

Properties of the CAM product do not suggest a problem with the combination used. No appropriate reports of interactions between the CAM product and the conventional medicine (or drug class) were found in the literature.

Theoretical

One or more isolated case reports of adverse interactions with the conventional medicine used (or drug class) were published or the pharmacological properties of the CAM product predict a potential interaction. The CAM product causality was not obvious from a review of the literature.

Significant

Reasonable evidence exists of a specific CAM product being causal in a reported adverse drug interaction or clinical studies demonstrate a significant adverse interaction potential. In some cases interaction potential was listed as significant when the CAM-drug combination involved both having properties, that when combined, had a significant chance for an adverse interaction. For example, the combination of pentoxifylline and ginkgo was determined to have a significant risk for a bleed even though an adverse interaction has not been well documented. Potential interactions assessed as significant were listed as pharmacodynamic interactions (additive or subtractive pharmacological properties) or pharmacokinetic interactions (effects on absorption, distribution, metabolism or excretion).

Simple descriptive statistics were used to show the use of medications in each time period. Differences in the prevalence of use of selected CAM substances between African American and white participants were examined using chi-square tests.

RESULTS

The study population consisted of 5,052 CHS participants who had at least one annual medication interview during the four time periods of the study (1994,1995,1997,1999); a total of 16,173 medication interviews were conducted. Participants ranged in age from 65 to 102 with the median age being 75 at the 1994 examination. There were 3,043 (60.2%) female, 2,009 male, 838 (16.6%) African-American, and 4,214 (83.4%) white participants. In the four time periods of the drug and CAM survey, over 89% of the participants were taking a prescription drug (Table 1). CAM product use increased during the study period. At the start of the survey, about 6% of participants were using CAM products while at the end, use was 15%.

The most common CAM products used by participants in our study (Table 2) are generally similar to those reported recently from the Slone survey1 and a report by Blumenthal[7] with garlic, ginkgo, and ginseng in the top seven most commonly used products. Some differences in use of individual CAM products between African Americans and whites in the study were evident. Among the seven most popular CAM products, African-American study participants used significantly more garlic ($p = .003$) and cod liver oil/fish oil ($p < .001$) and less glucosamine and lecithin ($p \leq .001$ for both). There was not a significant difference between African Americans and whites in the use of ginseng, gingko, or CoQ10 at the $p < .01$ level.

Table 3 shows combinations of CAM and conventional drugs used by the study participants that are considered to have significant potential for adverse consequences. Of the 5,052 study participants, 294 (5.8%) took combinations considered to have a significant risk for an adverse interaction. Among the 16,173 interviews conducted, there were 393 (2.4%) observed instances of these combinations. The most common combinations with significant risk involved garlic or ginkgo taken with aspirin, warfarin or antiplatelet adhesion drugs. These represented 379/393 (96%) of the situations with risk.

CAM product-drug combinations of less risk or less well documented risk for adverse effects were numerous (Table 4). There were 667 study participants taking these combinations and 786 occurrences of combinations. CAM products described in the literature as affecting platelet aggregation or decreasing blood coagulation are considered to have a potential interaction when combined with aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), warfarin or gemfibrozil. Combinations that could lead to risks for bleeds comprise 382/786 (49%) of the potential interactions and garlic or ginkgo combinations with conventional drugs accounted for 364 of these combination that were considered to have a theoretical risk. There were also 6 occurrences of glucosamine and glucosamine/chondroitin taken together with warfarin which could theoretically increase INR. and 8 occurrences of glucosamine taken with hypoglycemic drugs (data not shown). However, recent clinical evidence indicates an adverse interaction is unlikely with these combinations.

DISCUSSION

This study may be the first population based analysis of the prevalence of concurrent CAM medication-conventional medication combinations with an evaluation of the risk of adverse interactions for individual combinations. Both CAM-OTC combinations and CAM-prescription drug combinations were evaluated. The study participants were an older population (65 and older) on Medicare and almost all (>89%) were taking at least one prescription product. CAM use increased from 6% at the beginning to about 15% at the end of the study. This prevalence of CAM product use is consistent with that found for CAM product use in the general population by the Slone survey[1] (14%) and a survey by Tindle et al. (19%). 22 Many CAM product-prescription drug or CAM product-OTC drug combinations were identified with 14.4% of participants taking both a CAM product together with a conventional medication.

Some of these combinations were considered as having a risk for an adverse interaction. Individuals taking combinations considered to have a significant risk of an adverse interaction numbered 294 (5.8%) with garlic or ginkgo combinations with drugs affecting blood coagulation, such as aspirin, representing over 95% of the list of significant interactions. This reflects the high prevalence of use of these two herbals and the described risks for bleeds with use of these two supplements.[8–14] Several other observed CAM product-drug combinations were considered potentially dangerous. The highest risk combinations were judged to be the combination of garlic or ginkgo and warfarin, the combination of ginseng and warfarin, and the combination of St. John’s wort with digoxin. Both warfarin and digoxin have a narrow

therapeutic range and any modulations in drug levels can be disastrous. Garlic and ginkgo could increase the risk for a bleed with concurrent warfarin therapy due to the antiplatelet adhesion activities of the two herbals. 9–11,14 Panax quinquifolius ("American" ginseng) has been shown to induce CYP2C9 and thus would have the potential of decreasing warfarin benefit15,16 because the more potent enantiomer, S-warfarin, is metabolized by this isoform. We have no information in our study whether participants were taking Panax quiquifolius or Panax ginseng (Asian ginseng). Panax ginseng apparently does not significantly affect S-warfarin clearance.23 Digoxin is eliminated in large part by p-glycoprotein and St. John's wort is a strong inducer of this transporter.19;20 Although recent studies examining the effect of ginkgo on warfarin INR values (a measure of how quickly blood clots) indicate a lack of influence,24;25 the numbers of volunteers involved were small and CYP2C9 expression is influenced by genetic polymorphism. Larger ginkgo studies are needed to rule out risk. Of the more speculative CAM product-drug interactions, 382/786 (49%) involved the combination of a CAM product reported to have the potential to decrease blood coagulation with a drug that inhibited platelet adhesion, usually aspirin or an NSAID. The actual extent of risk is unknown.

Overall, most of the listed CAM-drug combinations with some risk for adverse interactions were considered pharmacodynamic with additive pharmacological effects. With the exception of St. John's wort, important pharmacokinetic CAM product-drug interactions are poorly defined in humans. While many CAM products inhibit CYP in vitro, few have been shown to broadly induce or inhibit the metabolism of concurrently administered drugs in vivo. St. John's wort is an exception, being a strong inducer of CYP3A4, CYP2E1, and Pgp in vivo.[19;23;26]

Although a strength of our study is that participants physically presented all CAM products and all conventional medications taken the previous two weeks to a study team member for recording, other desirable information was limited. We do not have information on the doses taken, the prevalence of use during the evaluation period, or whether the CAM and conventional medications were taken simultaneously on each consecutive day during that time. A further limitation is that the paucity of studies to definitively define adverse CAM product-drug interactions limited our ability to accurately assign risk to many of the various combinations. Futhermore, negative efficacy studies containing toxicity data may not get published. Although our survey was conducted in the years 1994, 1995, 1997 and 1999, recent surveys[1;7] show that the ranking of the most popular CAM products have changed very little. Garlic, ginkgo, and ginseng remain at or near the top of the rankings. We would have liked to have evaluated clinical outcomes such as hospitalization for bleeding. Because of the low frequency of these events, even for patients on warfarin, our sample did not have the power to permit this evaluation.

Given the equivocal evidence for efficacy and the potential risks for bleeds, the use of CAM products affecting blood coagulation may not be prudent in older patients taking conventional medications that affect clotting. A meta analysis of randomized trials from 1966–2000 showed only small, short term benefits of garlic supplements on lipids and antiplatelet adhesion activity.[27] Similarly, evidence for efficacy of ginkgo for age related dementia has been mixed.[28;29]

As of 2006 Medicare enrollees now have an insurance benefit for prescription drugs that will reduce out-of-pocket costs. This subsidy may increase the use of prescription drugs by seniors. Because the use of multiple conventional medications and the cost of dealing with their side effects is already a significant problem,[30] Medicare should study the use of pharmaceuticals and the safety of these conventional combinations. Having more disposable income may also lead to even more discretionary spending on CAM supplements. The already high prevalence of use by this older population of conventional medications together with CAM products points out the importance conducting studies to evaluate adverse interaction risks. All health care professionals need to be knowledgeable on the efficacy of CAM products when compared to

conventional medicines for the same indication. Then they can effectively communicate to patients about the optimal balance of CAM and conventional medications.

Larger volunteer studies in older adults to quantitate the potential for adverse drug CAM product interactions are clearly needed. Post-marketing surveillance may also be indicated. Of highest priority is to determine the risk of combining aspirin with ginkgo or garlic because many older adults take a daily aspirin in order to prevent stroke and emboli.[3] Until the results of these clinical studies are known, healthcare providers should inquire about patient use of CAM products and advise caution when they are used concurrently use with conventional drugs.

SUMMARY

A retrospective analysis of a Medicare population revealed that concurrent conventional and CAM product use was common. At year four of the study 15.1% of the population used CAM products and 14.4% concurrently were taking conventional medications and 5.8% were taking combinations considered to have a significant potential risk for an adverse interaction. Most of the combinations with risk involved concurrent use of CAM products with a risk for bleeding (especially ginkgo and garlic) together with conventional drugs taken to reduce blood clotting (especially aspirin). This study reveals the importance of undertaking studies to define the actual risk of taking garlic and ginkgo with aspirin in an older population.

Acknowledgments

This publication was made possible by Grant Number R03- AT002226 from the National Institutes of Health, National Center for Complementary and Alternative Medicine. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Center for Complementary and Alternative Medicine, National Institutes of Health.

References

1. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. JAMA 2002;287:337–44. [PubMed: 11790213]
2. Arnold AM, Psaty BM, Kuller LH, et al. Incidence of cardiovascular disease in older Americans: the cardiovascular health study. J Am Geriatr Soc 2005;53:211–8.10.1111/j.1532-5415.2005.53105.x [PubMed: 15673343]
3. Psaty BM, Lee M, Savage PJ, Rutan GH, German PS, Lyles M. Assessing the use of medications in the elderly: methods and initial experience in the Cardiovascular Health Study. The Cardiovascular Health Study Collaborative Research Group. J Clin Epidemiol 1992;45:683–92. [PubMed: 1607909]
4. Natural Medicines Comprehensive Database. Natural Medicines Comprehensive Database. Therapeutic Research Faculty. [(accessed September 24, 2006)]. www.naturaldatabase.com
5. Review of Natural Products. 2006 [(accessed September 26, 2006)]. Review of Natural Products. Facts and Comparisonswww.factsandcomparisons.com
6. The Natural Products Encyclopedia. The Natural Products Encyclopedia. EBSCO Publishing; 2006 [(accessed September 26, 2006)]. www.consumerlab.com
7. Blumenthal M. The 2004 top selling herbal supplements in food, drug and mass market retail outlets. HerbalGram 2006;71:64.
8. Bordia A, Verma SK, Srivastava KC. Effect of garlic (Allium sativum) on blood lipids, blood sugar, fibrinogen and fibrinolytic activity in patients with coronary artery disease. Prostaglandins Leukot Essent Fatty Acids 1998;58:257–63. [PubMed: 9654398]
9. Burnham BE. Garlic as a possible risk for postoperative bleeding. Plast Reconstr Surg 1995;95:213. [PubMed: 7809259]

10. German K, Kumar U, Blackford HN. Garlic and the risk of TURP bleeding (letter). Br J Urol 1995;76:518. [PubMed: 7551902]
11. Rose KD, Croissant PD, Parliament CF, Levin MB. Spontaneous spinal epidural hematoma with associated platelet dysfunction from excessive garlic ingestion: a case report. Neurosurgery 1990;26:880–882. [PubMed: 2352608]
12. Chung KF, Dent G, McCusker M, Guinot P, Page CP, Barnes PJ. Effect of a ginkgolide mixture (BN 52063) in antagonising skin and platelet responses to platelet activating factor in man. Lancet 1987;1:248–51. [PubMed: 2880069]
13. Rosenblatt M, Mindel J. Spontaneous hyphema associated with ingestion of Ginkgo biloba extract (letter). N Engl J Med 1997;336:1108. [PubMed: 9091822]
14. Matthews MK Jr. Association of Ginkgo biloba with intracerebral hemorrhage. Neurology 1998;50:1933–34. [PubMed: 9633781]
15. Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. Am J Health Syst Pharm 1997;54:692–93. [PubMed: 9075501]
16. Yuan CS, Wei G, Dey L, et al. Brief communication: American ginseng reduces warfarin's effect in healthy patients: a randomized, controlled trial (letter). Ann Intern Med 2004;141:23–27. [PubMed: 15238367]
17. Skogh M. Extracts of Ginkgo biloba and bleeding or haemorrhage. Lancet 1998;352:1145–46. [PubMed: 9798614]
18. Vale S. Subarachnoid haemorrhage associated with Ginkgo biloba. Lancet 1998;352:36. [PubMed: 9800751]
19. Durr D, Stieger B, Kullak-Ublick GA, et al. St John's Wort induces intestinal P-glycoprotein/MDR1 and intestinal and hepatic CYP3A4. Clin Pharmacol Ther 2000;68:598–604.10.1067/mcp.2000.112240 [PubMed: 11180019]
20. Izzo AA. Drug interactions with St. John's Wort (Hypericum perforatum): a review of the clinical evidence. Int J Clin Pharmacol Ther 2004;42:139–48. [PubMed: 15049433]
21. Piscitelli SC, Burstein AH, Weldon N, Gallicano KD, Falloon J. The Effect of Garlic Supplements on the Pharmacokinetics of Saquinavir. Clin Infect Dis 34:234–238. [PubMed: 11740713]
22. Tindle HA, Davis RB, Phillips RS, Eisenberg DM. Trends in use of complementary and alternative medicine by US adults: 1997–2002. Altern Ther Health Med 2005;11:42–49. [PubMed: 15712765]
23. Jiang X, Williams KM, Liauw WS, et al. Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol 2004;57:592–99.10.1111/j.1365-2125.2003.02051.x [PubMed: 15089812]
24. Jiang X, Williams KM, Liauw WS, et al. Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol 2005;59:425–32.10.1111/j.1365-2125.2005.02322.x [PubMed: 15801937]
25. Engelsen J, Nielsen JD, Winther K. Effect of coenzyme Q10 and Ginkgo biloba on warfarin dosage in stable, long-term warfarin treated outpatients. A randomised, double blind, placebo-crossover trial. Thromb Haemost 2002;87:1075–76. [PubMed: 12083489]
26. Gurley BJ, Gardner SF, Hubbard MA, et al. Clinical assessment of effects of botanical supplementation on cytochrome P450 phenotypes in the elderly: St John's wort, garlic oil, Panax ginseng and Ginkgo biloba. Drugs Aging 2005;22:525–39. [PubMed: 15974642]
27. Ackermann RT, Mulrow CD, Ramirez G, Gardner CD, Morbidoni L, Lawrence VA. Garlic shows promise for improving some cardiovascular risk factors. Arch Intern Med 2001;161:813–24. [PubMed: 11268223]
28. Mix JA, Crews WD Jr. A double-blind, placebo-controlled, randomized trial of Ginkgo biloba extract EGb 761 in a sample of cognitively intact older adults: neuropsychological findings. Hum Psychopharmacol 2002;17:267–77.10.1002/hup.412 [PubMed: 12404671]
29. Solomon PR, Adams F, Silver A, Zimmer J, DeVeaux R. Ginkgo for memory enhancement: a randomized controlled trial. JAMA 2002;288:835–40. [PubMed: 12186600]
30. Committee on Identifying and Preventing Medication Errors. Medication errors: incidence and cost. In: Philip Aspden, JW.; Bootman, JL.; Cronenwett, LR., editors. Preventing medication errors: quality chasm series. Washington DC: The National Academies Press; 2007.

Table 1

Medication Use by Study Enrollees

	Study Period							
	1 (1994)		2 (1995)		4 (1997)		6 (1999)	
	n	%	n	%	n	%	n	%
Total Users of any Product	4,364	100.0	4,343	100.0	3,912	100.0	3,554	100.0
RX[a] Users	3,982	91.2	3,884	89.4	3,525	90.1	3,250	91.4
CAM[b] Users	277	6.3	293	6.7	501	12.8	537	15.1
Vitamin/Mineral Users	1,724	39.5	1,722	39.7	1,703	43.5	2,102	59.1
OTC[c] Users	2,630	60.3	2,716	62.5	2,258	57.7	2,217	62.4
Total Rx & CAM	237	5.4	241	5.5	408	10.4	465	13.1
Total CAM with any Conventional (Rx or OTC)	264	6.0	270	6.2	459	11.7	511	14.4

[a]RX: Prescription medication

[b]CAM : Complementary and alternative medicine, herbal product

[c]OTC: Over the counter preparation (excludes CAM products)

Table 2

Prevalence of the Top 20 Complementary and Alternative Medicine (CAM) Products by Race, Study Results and a National Comparison

CAM Product	All Study Participants [a] Overall percent for all analysis periods			All Study Participants [b] Percent restricted to last analysis period			NHIS 2002 Data [c] Percent for 2002		
	All (n=5,052)	African Am (n=838)	White (n=4,214)	All (n=3,544)	African Am (n=568)	White (n=2,986)	All (n=5,475)	African Am (n=620)	White (n=4,855)
Garlic	5.86	7.76	5.48	3.52	5.28	3.18	2.60	3.00	2.50
Ginkgo	4.20	3.34	4.37	4.28	3.35	4.45	1.90	1.00	2.00
Glucosamine	2.45	0.48	2.85	2.76	0.70	3.15	2.80	0.60	3.10
Fish Oil/Cod Liver Oil	2.28	4.66	1.80	1.21	2.11	1.04	1.40	1.10	1.40
Lecithin	1.92	0.36	2.23	1.15	0.35	1.31			
Ginseng	1.11	1.67	1.00	0.59	0.88	0.54	1.10	0.80	1.10
CoQ10	0.97	0.24	1.12	0.87	0.18	1.00			
Alfalfa	0.91	0.48	1.00	0.56	0.35	0.60			
Antioxidant	0.91	0.72	0.95	0.37	0.00	0.44			
Chromium picolinate	0.85	0.24	0.97	0.31	0.18	0.33			
Melatonin	0.65	0.48	0.69	0.42	0.35	0.44	0.60	0.30	0.60
Saw palmetto	0.65	0.36	0.71	0.56	0.00	0.67	1.10	0.20	1.20
Echinacea	0.61	0.84	0.57	0.39	0.53	0.37	2.80	0.80	3.10
Aloe	0.53	0.48	0.55	0.37	0.00	0.44			
St. John’s wort	0.51	0.24	0.57	0.59	0.35	0.64	0.70	0.20	0.80
Chromium	0.49	0.36	0.52	0.23	0.18	0.23			
Bilberry	0.48	0.24	0.52	0.31	0.18	0.33			
L-lysine	0.42	0.12	0.47	0.25	0.00	0.30			
Bee pollen	0.36	0.36	0.36	0.14	0.35	0.10	0.60	0.30	0.70
Shark cartilage	0.32	0.36	0.31	0.20	0.18	0.02			

[a] Study Cohort: Used CAM product at least once over the four analysis years n=5,052 for all participants; n=838 for African Americans; n=4,214 for whites

[b] Study Cohort: Used CAM product in last analysis year 1998–1999 n=3,554 for all participants; n=568 for African Americans ; n=2,986 for whites

[c] 2002 National Health Information Survey (excluded participants under 65 and those who responded with unknown or refused to ever having used a natural herb for own health or treatment): n=5,475 for all participants; n=620 for African Americans; n=4,855 for whites. Participants were asked about the use of 35 natural herbs; data was included above where a surveyed herb matched one of the top 20 from the study

Table 3

Significant Risk of Adverse Event

Event Risk	Mechanism[a]	Number Using[b]		Total Prevalence[c]	
		n	%	n	%
Bleeds					
Aspirin					
Garlic[8–11]	PD	147	2.91	214	1.32
Ginkgo[12,13]	PD	102	2.02	127	0.79
Warfarin					
Garlic[9–11]	PD	13	0.26	16	0.10
Ginkgo[14]	PD	7	0.14	7	0.04
Ginseng[15,16]	CYP2C9 induction	3	0.06	3	0.02
Ticlopidine					
Garlic[8–11]	PD	4	0.08	6	0.04
Ginkgo[12,17,18]	PD	2	0.04	3	0.02
Pentoxifylline					
Ginkgo[12,17,18]	PD	3	0.06	3	0.02
Total		281	5.56	379	2.34
Decreased drug benefit					
Digoxin/St. John’s wort[19;20]	PGP induction	2	0.04	2	0.01
Felodipine/St. John’s wort[19]	CYP3A4 induction	2	0.04	2	0.01
Tamoxifen/Garlic[21]	CYP3A4 induction	4	0.08	5	0.03
Total		8	0.16	9	0.06
Other					
Furosemide/Aloe (hypokalemia)[4]	PD	3	0.06	3	0.02
Thyroid/Kelp (hyperthyroidism-elevated iodine)[4]	PD	2	0.04	2	0.01
Total		5	0.10	5	0.03
Grand Total		294	5.82	393	2.43
Garlic interactions:		168	3.33	241	1.49

Event Risk	Mechanism[a]	Number Using[b]		Total Prevalence[c]	
		n	%	n	%
Ginkgo interactions:		114	2.26	140	0.87
Garlic or ginkgo:		282	5.58	381	2.36

[a] PD = pharmacodynamic interaction, i.e., additive pharmacological effects

CYP2C9 = cytochrome P450 2C9

PGP = P-glycoprotein

CYP3A4 = cytochrome P450 3A4

[b] The number of unique individuals using the combination. Percents based on the 5,052 study participants.

[c] The observed prevalence of concurrent use. Percents based on the 16,173 interviews conducted.

Table 4

Possible or Theoretical Risk of Adverse Event[a]

Event Risk	Number Using[c]		Total Prevalence[d]	
	n	%	n	%
Bleeds (pharmacodynamic interaction[b])				
Aspirin with: Aloe (7, 7), bilberry (11, 13), capsaicin (3,3), cayenne (4, 4), cod liver oil (47, 63), fish oil (19, 22), flax seed oil (2, 2), ginger (2, 2), ginseng (26,32), grapeseed (8, 10), kelp (5, 5), melatonin (16, 18), papaya (3, 4), Pau d'arco (2, 3), evening primrose oil (2, 2), proanthocyanidin (2, 2), pycnogenol (2, 2)	161	3.19	194	1.20
NSAIDs with: Aloe (3, 3), cayenne (2, 2), Cod liver oil (21, 28), fish oil (4, 4), garlic (65, 73), ginkgo (55, 61), melatonin (4, 4), Pau d'arco (2, 3)	156	3.09	178	1.10
Warfarin with: Chondroitin (2, 2), Glucosamine/chondroitin (4, 4)	6	0.12	6	0.04
Gemfibrozil with: Garlic (3,4))	3	0.06	4	0.02
Total	326	6.45	382	2.36
Elevated drug effect (pharmacodynamic interaction†)				
Oral hypoglycemics with: Chromium (8, 9), Ginkgo (6, 6), Ginseng (2, 2)	16	0.32	17	0.11
Antihypertensives with: Cod liver oil (72, 81), CoQ10 (30, 34), Fish oil (4, 4), Melatonin (5, 5)	111	2.20	124	0.77
Total	127	2.51	141	0.87
Decreased drug effect (CYP3A4 induction)				
Garlic with (CYP3A4 substrates only): Antihypertensives (84, 106), "statins" (35,41), diazepam(3,4) erythromycin (3,4), carbamazepine (2,4), alprozolam (2,4), quinine sulfate (9,12)	138	2.73	175	1.08
St. John's Wort with antihypertensives (6,6)	6	0.12	6	0.04
Total	144	2.85	181	1.12
Decreased drug effect (CYP2C19 induction)				
Ginkgo with: Omeprazole (14,16), Amitriptyline (5,5), Propanolol (3,5), Diazepam (2,2)	24	0.48	28	0.17
Decreased drug effect (unknown mechanism)				
Ginseng with: furosemide (9,9), opioids (2,2)	11	0.22	11	0.07
Increased drug levels (CYP3A4 inhibition?)				
Ginkgo with nifedipine (13,15)	13	0.26	15	0.09
Ginseng with nifedipine (5,5)	5	0.10	5	0.03
Total	18	0.36	20	0.12
Other				
Conjugated estrogens/alfalfa (estrogen overload) (8, 13)	8	0.16	13	0.08
Digoxin/CoQ10 (narrow digoxin margin of safety) (3, 3)	3	0.06	3	0.02
Methotrexate/garlic (narrow methotrexate margin of safety) (2, 2)	2	0.04	2	0.01
Furosemide/Herbalax (licorice) (hypokalemia risk) (4, 5)	4	0.08	5	0.03
Total	17	0.34	23	0.14
Grand Total	667	13.20	786	4.86
Garlic interactions:	208	4.12	254	1.57
Ginkgo interactions:	98	1.94	110	0.68
Garlic or ginkgo	306	6.06	364	2.25

[a] For the parenthetical numbers, the first number is the count of unique individuals using the combination. The second number is the observed prevalence of concurrent use.

[b] additive pharmacological effects

[c] The number of unique individuals using the combination. Percents based on the 5,052 study participants.

[d] The observed prevalence of concurrent use. Percents based on the 16,173 interviews conducted.