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Factors Associated with Potential Medication-Herb/Natural Product Interactions in a Rural Community

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Abstract

Context—Use of both conventional medicines and herbs/natural products are increasing in the United States (US). Consequently, individuals are more likely to be exposed to potentially harmful interactions between these products.

Objective—To examine the use of both herbs/natural products and conventional medications in a rural community; examine the prevalence of potential interactions between herbs/natural products and conventional medications; and identify factors associated with exposure to such interactions.

Design—Population-based epidemiological study.

Setting—Data for this paper were collected between 1999 and 2004 as part of the *Johnston County Osteoarthritis Project*.

Participants—Limited to civilian, non-institutionalized, Caucasian and African American residents, age 45 years or older, of Johnston County, North Carolina. Data used in this paper are from 2,523 individuals who completed face-to-face interviews.

Main Outcome Measures—Prevalence of herb/natural product use and exposure to potential interactions between these products and conventional medications.

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Results—Nineteen percent (n=488) of participants used at least one herb/natural product. Among those who used both conventional medications and herbs/natural products, more than 1 in 5 (97 [21.9%]) were using a combination of products associated with a potential interaction. Odds of exposure to a potential interaction was lower among people who had health insurance and increased with the number of products used.

Conclusions—Many people are exposed to potential interactions between herbs/natural products and conventional medications. Research is needed to better understand the effect such interactions may have on patient care.

Introduction

Use of herbs and natural products has increased dramatically over the past 20 years in the United States. In a nationally representative telephone survey conducted in 1991, 2.5% of respondents reported having used an herb within the past year, compared to 12.1% of respondents in a parallel survey conducted in 1997.(1) This reflects a nearly 5-fold increase in herb use over a 6-year period. Data from the 2007 National Health Interview Survey confirms this increase in herb use with 17.7% of respondents reporting having used a nonvitamin, nonmineral, natural product within the past 30 days.(2) Similarly, in data collected between 1998 and 2004 as part of the Slone Survey, 17% of respondents reported using an herb or natural product within the past week.(3)

During this same time period, the use of prescription medications has continued to grow. Between 1997 and 2004, expenditures for outpatient prescription medications in the United States increased from $72.3 billion to $191.0 billion.(4) Data from the National Health and Nutrition Examination Survey (NHANES) indicate that, among all Americans, reported use of at least one prescription medication during the previous month increased from 39.1% in the period from 1988-1994 to 46.7% in the period from 2001-2004.(5) Use of multiple medications has also increased. During the period from 2001-2004, 20.2% of all Americans reported having used three or more prescription medications during the past month, compared to 11.8% who reporting doing so in the period from 1988-1994.(5) Moreover, medication utilization increased with age. During the period from 2001-2004, 59.6% of individuals age 65 and older reported using three or more prescription medications in the past month.

As the use of herbs/natural products and prescription medications increases, the likelihood that individuals may be exposed to potentially harmful interactions between these products increases as well. In a recent study focused on older adults (median age 75), Elmer and colleagues found that 5.8% were taking a combination of herbs/natural products and prescription medications considered to pose a significant risk for adverse events. (6) An additional 13.2% of participants were taking a combination of products associated with a theoretical or uncertain risk of adverse events. Others have observed even higher rates of potential interactions.(7)

Although many studies have examined factors associated with the use of herbs/natural products, only a few have examined the prevalence of interactions between these products and conventional medications.(6, 7) Moreover, we are not aware of any studies that have

attempted to identify factors associated with exposure to such interactions. Thus, in this paper, we report findings on the use of both herbs/natural products and conventional medications (prescription and over-the-counter) in a rural, Southern community. We also examine the prevalence of potential interactions among these products and identify factors associated with exposure to such interactions.

Methods

Study Design and Participants

Data were collected between 1999 and 2004 as part of an ongoing, federally-funded, population-based epidemiological study called the *Johnston County Osteoarthritis Project*. To be eligible, individuals had to be: civilian, non-institutionalized, Caucasian or African American, age 45 years or older, a resident of one of six selected townships in a rural county in the southeastern United States, and physically and mentally capable of completing study procedures. African Americans were purposively oversampled.

Two cohorts were recruited as part of the Johnston County project. The original cohort was recruited using population-based random sampling methods from 1991-1997. A second cohort was recruited in 2003-2004 to enrich the sample for African Americans and younger individuals who were deliberately targeted for inclusion. A detailed description of the sampling design and study protocol has been published previously.(10) Data used in this paper are from follow-up interviews of 1,571 individuals from the original cohort and initial interviews involving 952 individuals from the second cohort. The study was approved by the Institutional Review Boards of the School of Medicine at the University of North Carolina at Chapel Hill and the Centers for Disease Control and Prevention.

Data Collection Methods

All data were collected via face-to-face interviews. Most interviews were conducted in participants' homes. Before beginning the interview, interviewers described the study to participants, answered participant questions about the study, and obtained written informed consent to participate. Interviews were conducted with the aid of a laptop computer that contained all instructions and questionnaires. All questionnaires were administered orally. Each interview lasted an average of 90 minutes.

Measures

Utilization of Herbs and Natural Products—To assess the utilization of herbs and natural products, participants were read a list of 51 products and, for each product, asked to indicate whether or not they had used the product within the previous year. The list included herbs and botanical products (e.g., garlic, aloe vera), natural products obtained from animal sources (e.g., cod liver oil), natural hormones (e.g., phytoestrogen pills), and foods that are sometimes consumed for medicinal purposes (e.g., raisins soaked in gin or vodka). A complete list of the products assessed is included in the Appendix. Participants were also asked if they used any products other than those listed and, if so, to specify the products used. This information was used to create two variables, (1) a dichotomous variable indicating whether any herbs or natural products were used during the past year (0=No,

1=Yes) and (2) a continuous variable indicating the number of different herbs and natural products used. (Although use of vitamins (e.g., multivitamins, Vitamin C) and mineral products (e.g., calcium, zinc) was also assessed, vitamins and minerals were not included in variables assessing herb and natural product use.)

Utilization of Prescription and Over-the-Counter Medications—Participants were asked to retrieve all of the prescription and over-the-counter (OTC) medications that they were currently using. Medications used on either a regular or an as needed (PRN) basis were included. The interviewer reviewed the medications with each participant and recorded the name and strength for each medication. For the analyses reported in this paper, information concerning prescription and OTC medications was separated and a total of four variables were created. First, two dichotomous variables were created indicating whether the participant used any (1) prescription or (2) OTC medications. Second, two continuous variable were created to capture the number of different (1) prescription and (2) OTC medications used.

Potential Medication-Herb/Natural Product Interactions—Potential interactions between conventional medications and herbs/natural products used by study participants were determined by collecting and evaluating interaction data from three sources: Natural Medicines Comprehensive Database (online; professional version)(11), Office of Dietary Supplements website(12), and the National Center for Complementary and Natural Medicine.(13) Interactions were included if supporting data included clinical trials, pharmacokinetic studies, or documented case reports involving a specific drug or class of drug. The potential severity associated with each type of interaction was noted using the ratings included in the Natural Medicines Comprehensive Database.(11) Four levels of severity are indicated in the database: (1) insignificant (drug levels may be affected, but a clinically significant interaction is not likely); (2) mild (mild impairment or mild discomfort possible); (3) moderate (moderate impairment or significant discomfort possible), and (4) high (life threatening or severe impairment possible). Potential interactions were excluded if supporting data were based only on *in vitro* or animal model research. Theoretical interactions were also excluded.

Health Insurance Status—Insurance status was coded as a dichotomous variable (0=No insurance or Medicare Part A only, 1=Insurance other than or in addition to Medicare Part A). This dichotomous coding was used because individuals with no insurance or only Medicare Part A have no coverage for outpatient services.

Health Status—Four health status indicators were assessed: disability, depressive symptoms, fatigue, and comorbidities. Disability was assessed using the 20-item Health Assessment Questionnaire (HAQ).(14) Participants rate the degree of difficulty they experience performing different activities of daily living using a 4-point scale ranging from 0=*Able to do without any difficulty* to 3=*Unable to do*. Items are grouped into eight categories and category scores are adjusted for the need for assistance from others or the use of assistive devices. An overall disability index is calculated by averaging across the eight categories, with the overall index having a possible range of 0 to 3. (15, 16)

The presence of depressive symptoms was assessed using the 20-item Center for Epidemiological Studies-Depression (CES-D) scale.(17) Participants rate the frequency with which they have experienced a particular symptom during the previous week. Responses were recorded on a 4-point scale ranging from 0=*Rarely or none of the time* to 3=*Most or all of the time*. Responses are summed across items to yield an overall score with a possible range of 0 to 60. The CES-D is widely-used to assess the presence of depressive symptoms in both community and patient samples.(18)

Participants rated how much of a problem unusual fatigue or tiredness had been in the past week using a visual analogue scale. Scale endpoints were labeled 0=no problem and 100=major problem.(19, 20)

To assess comorbidities, participants were asked if they were currently experiencing, or had experienced in the past, any of 47 different conditions. This information was used to create an index based on the Charlson Comorbidity Index.(21) Ten types of conditions were included in this index: chronic lung problems (e.g., bronchitis, emphysema, asthma), stroke, myocardial infarction, stomach ulcer, Alzheimer's disease, rheumatoid arthritis, dialysis or kidney failure, paralysis of any kind, cancer, and diabetes. Each of the first six conditions was scored as “1” if it was currently present. A past history of either myocardial infarction or stroke was also scored as “1” each. Based on weights recommended by Charlson, the last four conditions were each scored as “2” if they were currently present.(21) The Charlson weights reflect the relative risk of 1-year mortality among people with a particular condition versus those without the condition. This variable had a possible range of 0 to 14.

Sociodemographic Characteristics—Sociodemographic characteristics included: age, gender (Male, Female), race (Caucasian, African-American), and education (High school or less, At least some college). This information was collected via self-report.

Statistical analyses—Descriptive statistics were used to describe the characteristics of study participants and the utilization of herbs/natural products and prescription/over-the-counter medications. T-tests and Chi-square tests were used for demographic and clinical comparisons between the cohorts. Chi-square tests were used to evaluate differences in the utilization of herbal products across sample subgroups. To examine factors associated with exposure to potential medication-herb interactions, the sample was restricted to individuals who used at least one herb/natural product and at least one prescription/OTC medication. Unadjusted odds ratios were computed for each predictor variable (i.e., health insurance status, disability, depressive symptoms, fatigue, number of comorbidities, age, education, race, gender, number of herbs/natural products used, number of prescription/OTC medications used, and cohort membership). The predictor variables were selected to include: (1) demographic characteristics that have been associated with the use of herbs/natural products, (2) health status characteristics that may result in greater need for conventional medications or herbs/natural products, and (3) measures reflecting the number of herbs/natural products and conventional medications used. To control for potential confounding, adjusted odds ratios were computed via a logistic regression model that controlled for all of the predictor variables. Due to missing data, the sample size for the full model was 419.

Model fit was assessed by the Hosmer-Lemeshow Goodness-of-Fit test.(22) All analyses were conducted using PC SAS version 9.1.(23)

Results

The full sample included 2523 individuals. Characteristics of study participants are shown in Table 1. Compared to participants in the original cohort (N=1571), participants in the second cohort (N=952): were younger (Means=59.5 years (SD=10.5) versus 65.8 years (SD=9.78), $p < 0.0001$); were less likely to have completed some college (24.3% versus 29.4%, $p < 0.006$) or have health insurance (89.1% versus 94.4%, $p < 0.0001$); used more prescription medications (Means=4.2 (SD=3.1) versus 3.9 (SD=2.7), $p < 0.02$); used more OTC medications (Means=0.9 (SD=1.0) versus 0.79 (SD=0.9), $p < 0.0001$); were more likely to be African-American (41.3% versus 28.1%, $p < 0.0001$); and reported more disability (Means=0.60 (SD=0.66) versus 0.44 (SD=0.63), $p < 0.0001$), depressive symptoms (Means=8.8 (SD=10.0) versus 5.3 (SD=7.1), $p < 0.0001$), and fatigue (Means=19.4 (SD=31.6) versus 15.8 (SD=27.3), $p < 0.01$). The two cohorts were similar in terms of gender, number of comorbidities, and number of herbs/natural products used.

Use of Herbs/Natural Products

As shown in Table 2, 19.3% (n=488) of the individuals in the full sample used at least one herb or natural product. Among these individuals, the number of products used ranged from 1 to 20. However, most of these individuals (60.7%, n=296) used only one product. A little over 10% of herb/natural product users (n=51) used more than three products. The most commonly used herbs/natural products were: garlic (4.9%); glucosamine and/or chondroitin (3.2%); vinegar, honey, and cranberry juice or a combination of these (2.9%); and fish oils (2.4%). Subgroup comparisons indicated that herb/natural product use was more prevalent among women, Caucasians, and individuals with some college, compared to men, African-Americans, and individuals with no more than a high school education, respectively.

Prevalence of Potential Medication – Herb/Natural Product Interactions

Of the 488 people who used one or more herbs/natural products, 443 (90.8%) also used at least one prescription/OTC medication, with all but 25 of these individuals using at least one prescription medication. The prescription/OTC medications most commonly used by herb/natural product users are shown in Table 3. Relatively few people were using medications such as warfarin (n=6) and digoxin (n=12) that have a narrow therapeutic index.

Among the 443 people using at least one prescription/OTC medication and at least one herb/natural product, 97 (21.9%) different individuals were using a combination of products associated with a potential interaction, representing 3.8% of the full sample. A total of 168 potential interactions were identified. As shown in Table 4, 115 of the 168 potential interactions (68.5%) involved garlic and cytochrome P450 3A4 substrates (e.g., amlodipine, atorvastatin, simvastatin, verapamil). Although the severity of most of the 168 potential interactions was classified as “Moderate”, 27 (16.1%) were classified as “High” in severity.

Table 5 shows the results of bivariate and multivariate logistic regression analyses predicting exposure to a potential medication-herb/natural product interaction among individuals using

at least one prescription/OTC medication and at least one herb/natural product. The bivariate analyses indicate that the odds of exposure to a potential interaction increases with increases in: fatigue, number of comorbidities, number of herbs used, number of OTC medications used, and number of prescription medications used. In addition, individuals with health insurance were less likely to be exposed to a potential interaction than those without health insurance. Four of these variables remained statistically significant in the multivariate model: number of herbs used, number of OTC medications use, number of prescription medications used, and insurance status. In addition, disability was statistically significant in the multivariate model with the odds of exposure to a potential interaction lower among people with greater levels of disability. The Hosmer and Lemeshow goodness-of-fit test indicated that the final model provided a reasonable fit to the data (χ^2 (8)=4.35, p=.82).

Discussion

Nearly 1 in 5 (19.3%) study participants used at least one herb/natural product, similar to that reported in recent national surveys.(2 3, 9) Consistent with past research, we too observed that women(3, 9, 49), Caucasians(2, 3, 9), and better educated individuals(3, 9, 49) were more likely to use these products.

Among individuals using at least one herb/natural product, almost all also used at least one prescription/OTC medication, and among these individuals, more than 1 in 5 (21.9%) were using a combination of products associated with a potential medication-herb interaction, representing 3.8% of the full sample. Although most of the identified potential interactions are considered of moderate severity, 27 are considered high in potential severity based on ratings included in the Natural Medicines Comprehensive Database.(11) These findings underscore the need to educate the public and health care providers about potential interactions between herbs/natural products and conventional medications. Further, our results highlight the need for physicians to ask patients about the use of herbs/natural products and to do so in a nonjudgmental way that encourages patients to provide accurate and complete information. Although we did not directly assess whether study participants had informed their health care provider about their use of herbs/natural products, previous research suggests that only about one in three people who use herbs/natural products report this information to their providers. (1, 8, 9) Thus, there is considerable need for improvement in this area.

Our findings also suggest that the risk of herb/natural product-conventional medication interactions is greater among individuals without health insurance and that the risk of interaction increases with the number of products used. Additional research is needed to confirm these findings in an independent sample. If confirmed, efforts directed at better understanding the nature of these relationships should be undertaken. For example, with respect to health insurance, research suggests that individuals without health insurance are more likely than others to forego needed medical care due to cost and to use herbs/natural products in an effort to self-manage their condition.(5) Thus, their use of herbs/natural products may be even less likely than others to be monitored by a health care provider. Future research should examine this possibility.

This study has strengths in its biracial, population-based sample of men and women, its inclusion of an extensive array of herbs/natural products, and its detailed assessment of potential herb/natural product-conventional medication interactions. Several study limitations must also be noted. First, the sample was limited to Caucasian and African American residents of a single county in North Carolina. Therefore, the generalizability of study findings to other areas and racial and ethnic groups will need to be established by future research. Second, all data concerning herb/natural product and conventional medication use were obtained by self-report. Thus, any factors that might cause patients to provide incomplete or inaccurate information would jeopardize the validity of our findings. Third, we do not know that study participants were using the products implicated in the potential interactions concurrently, which would be necessary for an interaction to occur. However, the limited information that is available in the literature suggests that many people, including health care providers, have limited knowledge concerning the potential for interactions between conventional medications and herbs/natural products.(50-53) Without this knowledge, individuals who use both types of products are unlikely to be able to coordinate their use in a way that minimizes the potential for interaction. Finally, information concerning herb/natural product-conventional medication interactions continues to evolve. Evidence of potential interactions comes from many sources ranging from clinical trials and pharmacokinetic studies to in vitro research. In this study, we relied primarily on the Natural Medicines Comprehensive Database (online; professional version) which is updated daily as new information on herb/natural product-conventional medication interactions emerges. To restrict the number of interactions identified to those that are more likely to be clinically meaningful, we considered only interactions identified on the basis of clinical trials, pharmacokinetic studies, or case reports. Many more interactions would have been identified had we included interactions supported solely by *in vitro* or animal model research or theoretical interactions based on knowledge of mechanisms of action. Nonetheless, we recognize that interactions supported only by case-report data must also be regarded with caution. In addition, we were not able to determine if the potential interactions identified in this study were associated with deleterious patient health outcomes in our study population. This is a major limitation of the current study and represents an important area for future research.

In conclusion, our findings underscore the growing use of herbs/natural products in the United States. The concomitant use of prescription and OTC medications with herbs/natural products exposes patients to potential interactions among these products. In our sample, more than 1 in 5 (21.9%) people who were using both herbs/natural products and prescription/OTC medications were taking a combination of products associated with a potential interaction. This represented 3.8% of the full sample. Although some interactions may result in an immediate, life-threatening adverse event (e.g., bleeding episode), the effects of other interactions may be more insidious. For example, due to enzyme induction, the effectiveness of a chronic medication may be reduced with the initiation of an herbal remedy. If the interaction goes unrecognized, the dose of the medication may be increased or the medication may be changed unnecessarily, exposing the patient to greater risk. Given the growing use of both herbs/natural products and prescription/OTC medications, our findings

suggest an urgent need to better understand the effects that medication-herb/natural product interactions may have on clinical practice and patient health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in natural medicine use in the United States, 1990-1997: results of a follow-up national survey. JAMA. 1998; 280(18):1569–1575. [PubMed: 9820257]
2. Barnes, PM., Bloom, B., Nahin, RL. National health statistics reports; no 12. Hyattsville, MD: National Center for Health Statistics; 2008. Complementary and alternative medicine use among adults and children: United States, 2007.
3. Kelly JP, Kaufman DW, Kelley K, Rosenberg L, Mitchell AA. Use of herbal/natural supplements according to racial/ethnic group. J Altern Complement Med. 2006; 2(6):555–61.
4. Stagnitti, MN. Statistical Brief #168. Agency for Healthcare Research and Quality; Rockville, MD: Apr. 2007 Trends in outpatient prescription drug utilization and expenditures: 1997 and 2004. http://www.meps.ahrq.gov/mepsweb/data_files/publications/st168/stat168.pdf
5. National Center for Health Statistics. Health, United States 2008 with Chartbook. Hyattsville, MD: 2008.
6. Elmer GW, Lafferty WE, Tyree PT, Lind BK. Potential interactions between complementary/natural products and conventional medicines in a Medicare population. Ann Pharmacother. 2007; 41(10): 1617–1624. [PubMed: 17785609]
7. Yoon SL, Schaffer SD. Herbal, prescribed, and over-the-counter drug use in older women: prevalence of drug interactions. Geriatr Nur (Lond). 2006; 27:118–129.
8. Canter PH, Ernst E. Herbal supplement use by persons aged over 50 years in Britain: frequently used herbs, concomitant use of herbs, nutritional supplements and prescription drugs, rate of informing doctors and potential for negative interactions. Drugs Aging. 2004; 21(9):597–605. [PubMed: 15260514]
9. Gardiner P, Graham R, Legedza AT, Ahn AC, Eisenberg DM, Phillips RS. Factors associated with herbal therapy use by adults in the United States. Altern Ther Health Med. 2007; 13(2):22–29.
10. Jordan JM, Helmick CG, Renner JB, et al. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. J Rheumatol. 2007; 34(1):172–180. [PubMed: 17216685]
11. Stockton (CA): Natural Medicines Comprehensive Database Professional Version [database on the Internet]. c1995-2008-[cited 2008 March]. Available from http://www.naturaldatabase.com
12. Bethesda (MD): Office of Dietary Supplements [homepage on the Internet]. Available from: http://ods.od.nih.gov
13. National Center for Complementary and Natural Medicine [homepage on the Internet]. Bethesda (MD): National Institutes of Health; [updated 2008 May 12]. Available from: http://nccam.nih.gov
14. Fries JF, Spitz P, Young D. The dimensions of health outcomes: the Health Assessment Questionnaire, disability and pain scales. J Rheumatol. 1982; 9:1780–1793.

15. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. J Rheumatol Jan. 2003; 30(1):167–178.
16. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: dimensions and practical applications. Health Qual Life Outcomes. 2003; 1:20. [PubMed: 12831398]
17. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. Applied Psychological Measurement. 1977; 1:385–401.
18. Blalock SJ, DeVellis RF, Brown GK, Wallston KA. Validity of the Center for Epidemiological Studies Depression Scale in arthritis populations. Arthritis Rheum. 1989; 32:991–997. [PubMed: 2765012]
19. Lorig, K., Stewart, AL., Ritter, P., Gonzalez, V., Laurent, D., Lynch, J. Outcome measures for health education and other health care interventions. Thousand Oaks (CA): Sage Publications; 1996.
20. Stewart, AL., Hays, RD., Ware, JE. Health perceptions, energy/fatigue, and health distress measures. In: Stewart, AL., Ware, JE., editors. Measuring functioning and well-being: The Medical Outcomes Study approach. Durham (NC): Duke University; 1992.
21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5):373–383. [PubMed: 3558716]
22. Hosmer, DW., Lemeshow, S. Applied Logistic Regression. 2nd. New York: John Wiley & Sons; 2000.
23. SAS Institute Inc. SAS/STAT 9.1. Cary, NC: SAS Institute Inc; 2001.
24. Piscitelli SC, Burstein AH, Welden N, et al. The effect of garlic supplements on the pharmacokinetics of saquinavir. Clin Infect Dis. 2002; 34:234–8. [PubMed: 11740713]
25. Gurley BJ, Gardner SF, Hubbard MA, et al. Cytochrome P450 phenotypic ratios for predicting herb-drug interactions in humans. Clin Pharmacol Ther. 2002; 72:276–87. [PubMed: 12235448]
26. Sunter WH. Warfarin and garlic. Pharm J. 1991; 246:722.
27. Kudolo GB. The effect of 3-month ingestion of Ginkgo biloba extract on pancreatic beta-cell function in response to glucose loading in normal glucose tolerant individuals. J Clin Pharmacol. 2000; 40:647–54. [PubMed: 10868316]
28. Kudolo GB. The effect of 3-month ingestion of Ginkgo biloba extract (EGb 761) on pancreatic beta-cell function in response to glucose loading in individuals with non-insulin-dependent diabetes mellitus. J Clin Pharmacol. 2001; 41:600–11. [PubMed: 11402628]
29. Yin OQ, Tomlinson B, Waye MM, et al. Pharmacogenetics and herb-drug interactions: experience with Ginkgo biloba and omeprazole. Pharmacogenetics. 2004; 14:841–50. [PubMed: 15608563]
30. Meisel C, Johne A, Roots I. Fatal intracerebral mass bleeding associated with Ginkgo biloba and ibuprofen. Atherosclerosis. 2003; 167:367. [PubMed: 12818420]
31. Galluzzi S, Zanetti O, Binetti G, et al. Coma in a patient with Alzheimer's disease taking low dose trazodone and Ginkgo biloba. J Neurol Neurosurg Psychiatry. 2000; 68:679–80.
32. Gregory PJ. Seizure associated with Ginkgo biloba? Ann Intern Med. 2001; 134:344.
33. Granger AS. Ginkgo biloba precipitating epileptic seizures. Age Ageing. 2001; 30:523–5. [PubMed: 11742783]
34. Roby CA, Anderson GD, Kantor E, et al. St John's wort: Effect on CYP3A4 activity. Clin Pharmacol Ther. 2000; 67:451–7. [PubMed: 10824623]
35. Schulz V. Incidence and clinical relevance of the interactions and side effects of Hypericum preparations. Phytomedicine. 2001; 8:152–60. [PubMed: 11315759]
36. Henderson L, Yue QY, Bergquist C, et al. St John's wort (Hypericum perforatum): drug interactions and clinical outcomes. Br J Clin Pharmacol. 2002; 54:349–56. [PubMed: 12392581]
37. Markowitz JS, Donovan JL, DeVane CL, et al. Effect of St John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. JAMA. 2003; 290:1500–4. [PubMed: 13129991]
38. Hakas JF Jr. Topical capsaicin induces cough in patient receiving ACE inhibitor. Ann Allergy. 1990; 65:322–3. [PubMed: 2221491]

39. Cheema P, El-Mefty O, Jazieh AR. Intraoperative haemorrhage associated with the use of extract of Saw Palmetto herb: a case report and review of literature. J Intern Med. 2001; 250:167–9. [PubMed: 11489067]
40. Becker BN. Ginseng-induced diuretic resistance. JAMA. 1996; 276:606–7.
41. Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. Am J Health Syst Pharm. 1997; 54:692–3. [PubMed: 9075501]
42. Gorski JC, Huang S, Zaheer NA, et al. The effect of echinacea (Echinacea purpurea root) on cytochrome P450 activity in vivo. Clin Pharmacol Ther. 2003; 73(Abstract PDII-A-8):94.
43. Rozenfeld V, Crain JL, Callahan AK. Possible augmentation of warfarin effect by glucosamine-chondroitin. Am J Health Syst Pharm. 2004; 61:306–307. [PubMed: 14986566]
44. Knudsen J, Sokol GH. Potential glucosamine-warfarin interaction resulting in increased international normalized ratio: Case report and review of the literature and MedWatch database. Pharmacotherapy. 2008; 28:540–8. [PubMed: 18363538]
45. Yue, QY., Strandell, J., Myrberg, O. Concomitant use of glucosamine may potential the effect of warfarin. The Uppsala Monitoring Centre; Available at: www.who-umc.org/graphics/9722.pdf [Accessed 28 April 2008]
46. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. Cochrane Database Syst Rev. 2002; 2:CD001520.
47. Iruela LM, Minguez L, Merino J, Monedero G. Toxic interaction of S-adenosylmethionine and clomipramine. Am J Psychiatry. 1993; 150:522.
48. Berlanga C, Ortega-Soto HA, Ontiveros M, Senties H. Efficacy of S-adenosyl-L-methionine in speeding the onset of action of imipramine. Psychiatry Res. 1992; 44:257–62. [PubMed: 1289923]
49. Gardiner P, Graham RE, Legedza AT, Eisenberg DM, Phillips RS. Factors associated with dietary supplement use among prescription medication users. Arch Intern Med. 2006; 166(18):1968–1974. [PubMed: 17030829]
50. Clement YN, Williams AF, Khan K, et al. A gap between acceptance and knowledge of herbal remedies by physicians: the need for educational intervention. BMC Complement Altern Med. 2005; 5:20. [PubMed: 16297236]
51. Vickers KA, Jolly KB, Greenfield SM. Herbal medicine: women's views, knowledge and interaction with doctors: a qualitative study. BMC Complement Altern Med. 2006; 6:40. [PubMed: 17156416]
52. Lederman VG, Huffman FG, Enrione EB. Knowledge of Florida nurses and dietitiansregarding dietary supplements. Complement Ther Clin Pract. 2009; 15:38–43. [PubMed: 19161954]
53. Temple MD, Fagerlund K, Saewyc E. A national survey of certified registered nurse anesthetists' knowledge, beliefs, and assessment of herbal supplements in the anesthesia setting. AANA J. 2005; 73:368–77. [PubMed: 16261853]

Table 1

Characteristics of Full Sample and Subset of Individuals Who Used At Least One Herb/Natural Product and At Least One Prescription/Over-the-Counter Medication

Characteristics	Full Sample (N=2523)†	Participants Who Used At Least One Herb/Natural Product and At Least One Prescription/Over-the- Counter Medication (N=443)‡
Mean Age, years (SD)	63.4 (10.5)	63.6 (9.9)
% Under 65	56.4	54.2
% Female	66.0	78.5
% African-American	33.0	24.6
% With Some College Education	27.5	33.3
% Health Insurance Coverage	92.4	93.6
Mean Disability Score (SD)	0.5 (0.6)	0.5 (0.7)
Mean Depression Score (SD)	6.6 (8.5)	7.5 (9.8)
Mean Fatigue Score (SD)	17.2 (29.0)	21.8 (31.3)
Mean # of Comorbidities (SD)	0.8 (1.1)	0.7 (1.1)
Mean # of Herbs/Natural Products Used (SD)	0.4 (1.2)	1.9 (1.9)
Mean # of Prescription Medications Used (SD)	3.6 (3.0)	4.0 (2.9)
Mean # of OTC Medications Used (SD)	0.7 (0.9)	0.8 (0.9)

† Due to missing data, N's=2519 for age; 2510 for education, 2521 for gender and race; and 2399 for health insurance, disability, depression, fatigue, and comorbidities.

‡ Due to missing data, N's=442 for education and 419 for health insurance, disability, depression, fatigue, and comorbidities.

Table 2

Frequency of the Use of Herbs/Natural Products

Herb/Natural Product		By Gender* % (n)		By Race* % (n)		By Age % (n)		By Education* % (n)	
	Overall (N=2523) % (n)	Women (n=1661)	Men (n=857)	African-American (n=831)	Caucasian (n=1687)	65+ (n=1099)	Under 65 (n=1420)	No College (n=1822)	Some College+ (n=691)
Any Herb or Natural Product	19.3 (488)	22.6 (375)	13.2 (113)	14.2 (118)	21.9 (370)	19.9 (219)	18.9 (269)	17.6 (320)	24.2 (167)
Garlic	4.9 (124)	5.5 (91)	3.9 (33)	5.2 (43)	4.8 (81)	5.8 (64)	4.2 (60)	5.1 (92)	4.6 (32)
Glucosamine and/or Chondroitin	3.2 (81)	3.3 (55)	3.0 (26)	0.6 (5)	4.5 (76)	3.4 (37)	3.1 (44)	2.7 (49)	4.6 (32)
Vinegar, honey, and cranberry juice or a combination of these	2.9 (73)	3.7 (61)	1.4 (12)	2.7 (22)	3.0 (51)	2.7 (30)	3.0 (43)	2.8 (51)	3.2 (22)
Fish Oils (Omega-3 Fatty Acids)	2.4 (61)	2.8 (46)	1.8 (15)	1.1 (9)	3.1 (52)	2.6 (29)	2.3 (32)	2.3 (42)	2.6 (18)
Cayenne Pepper	1.8 (45)	2.2 (36)	1.1 (9)	1.2 (10)	2.1 (35)	1.6 (17)	2.0 (28)	1.5 (27)	2.6 (18)
Cod Liver Oil	1.8 (45)	2.1 (34)	1.3 (11)	2.7 (22)	1.4 (23)	2.2 (24)	15 (21)	1.8 (33)	1.7 (12)
Aloe Vera	1.7 (43)	2.2 (36)	0.8 (7)	1.2 (10)	2.0 (33)	1.6 (18)	1.8 (25)	1.4 (25)	2.6 (18)
Ginkgo Biloba	1.5 (38)	1.8 (30)	0.9 (8)	0.4 (3)	2.1 (35)	1.2 (13)	1.8 (25)	0.9 (17)	3.0 (21)
Cranberry	1.3 (32)	1.7 (28)	0.5 (4)	0.6 (5)	1.6 (27)	1.3 (14)	1.3 (18)	1.2 (21)	1.6 (11)
Echinacea	1.0 (26)	1.2 (20)	0.7 (6)	0.7 (6)	1.2 (20)	0.4 (4)	1.6 (22)	0.4 (8)	2.6 (18)
Ginseng	1.0 (26)	1.2 (20)	0.7 (6)	1.1 (9)	1.0 (17)	0.8 (9)	1.2 (17)	1.0 (18)	1.2 (8)
Selenium	0.9 (22)	0.8 (13)	1.1 (9)	0.2 (2)	1.2 (20)	1.0 (11)	0.8 (11)	0.4 (8)	2.0 (14)
Phytoestrogen pills (soy or flax)	0.8 (21)	1.2 (20)	0.1 (1)	0.2 (2)	1.1 (19)	0.3 (3)	1.3 (18)	0.5 (9)	1.7 (12)
Chromium	0.8 (20)	0.9 (15)	0.6 (5)	0.6 (5)	0.9 (15)	0.4 (4)	1.1 (16)	0.7 (12)	1.2 (8)
St. John's Wort	0.7 (17)	1.0 (16)	0.1 (1)	0.5 (4)	0.8 (13)	0.4 (4)	0.9 (13)	0.5 (9)	1.2 (8)
Ginger	0.6 (16)	0.8 (13)	0.4 (3)	1.0 (8)	0.5 (8)	0.4 (4)	0.9 (12)	0.7 (12)	0.6 (4)
Saw Palmetto	0.6 (15)	0.1 (2)	1.5 (13)	0.1 (1)	0.8 (14)	0.4 (4)	0.8 (11)	0.4 (8)	1.0 (7)

*Between group difference in use of any herb or natural product statistically significant at $p < 0.001$.

Table 3

Therapeutic Classes of Medications Most Frequently Used By 433 Participants Also Using At Least One Herb/Natural Product

Therapeutic Class	Number of Users	Example of Medication in Class
Prescription Medications		
Beta-Adrenergic Blocking Agents	100	Metoprolol, Atenolol
HMG-CoA Reductase Inhibitors	99	Atorvastatin, Simvastatin
Estrogens	99	Conjugated estrogens
Proton Pump Inhibitors *	89	Omeprazole, Lansoprazole
Thiazide Diuretics	82	Hydrochlorothiazide
Angiotensin-Converting Enzyme Inhibitors	81	Lisinopril, Enalapril
Cycloxygenase-2 Inhibitors	65	Celecoxib
Second Generation Antihistamines *	56	Fexofenadine
Thyroid Agents	51	Levothyroxine
Over-The-Counter Medications		
Salicylates	150	Aspirin
Other Nonsteroidal Anti-Inflammatory Agents	90	Ibuprofen, Naproxen
Miscellaneous Analgesics and Antipyretics	60	Acetaminophen

* Although some proton pump inhibitors and second generation antihistamines may now be purchased without a prescription, these agents were available only by prescription during most of the data collection period.

Table 4

Potential Medication-Herb/Natural Product Interactions Observed Among 488 Participants Using at Least One Herb/Natural Product and at Least One Prescription or Over-The-Counter Medication*

Herb (# of Users)	# of People Exposed to Potential Interaction	Medication/ Medication Class (# of Interactions)	Severity	Comments
Garlic (124)	69	Cytochrome P450 3A4 Substrates (114)†	Moderate	Some garlic preparations appear to induce activity of CYP3A4 and reduce drug levels of substrates. However, results are inconsistent across studies. Until more is known, use caution when considering concomitant use of garlic and CYP3A4 substrates. (24-25)
		Dipyridamole (1)	Moderate	Compound found in garlic prevents platelet aggregation and might increase the risk of bleeding when combined with other antiplatelet agents.(26)
Ginkgo biloba (38)	17	Antidiabetes Drugs (7)‡	Moderate	Use of ginkgo may result in a significant worsening of glucose tolerance.(27-28)
		Omeprazole (3)	Minor	Use of ginkgo may decrease omeprazole levels. (29)
		Ibuprofen (2)	High	There has been a case report of intracranial hemorrhage in a patient taking ibuprofen and ginkgo. (30)
		Lansoprazole (2)	Moderate	Use of ginkgo may decrease lansoprazole levels.(29)
		Trazodone (2)	High	There has been a case report of coma in a patient taking trazodone and ginkgo. (31)
		Clonazapam (1)	High	Use of ginkgo may lower seizure threshold among people taking anticonvulsants.(32-33)
St. Johns Wort (17)	10	Cytochrome P450 3A4 Substrates (15)††	High	St. John's Wort induces cytochrome P450 3A4 and reduces drug levels of substrates. It should be avoided among patients using CYP3A4 substrates.(34-37)
Cayenne Pepper (45)	10	Angiotensin-Converting Enzyme (ACE) Inhibitors (10)‡‡	Mild	A case report suggests that topically applied cayenne pepper may contribute to ACE inhibitor-induced cough.(38)
Saw Palmetto (15)	4	Aspirin (4)	High	Concurrent use of saw palmetto and aspirin may increase bleeding risk and bleeding time.(39)
Ginseng (26)	2	Furosemide (2)	Moderate	There has been a case report of diuretic resistance in a patient taking furosemide plus a ginseng product containing other ingredients.(40)
		Warfarin (1)	Moderate	Concurrent use of ginseng may decrease the effectiveness of warfarin therapy.(41)
Echinacea (26)	1	Caffeine (1)	Mild	Use of echinacea may increase caffeine levels by 30%.(42)
Glucosamine and/or chondroitin sulfate (81)	1	Warfarin (1)	High	Increase INR following huge doses of glucosamine plus chondroitin.(43-45)
Melatonin (7)	1	Warfarin (1)	High	There have been case reports of minor bleeding and decreased prothrombin activity in people taking melatonin with warfarin.(46)
SAM-e (3)	1	Fluoxetine (1)	High	Concomitant use of these products may result in additive serotonergic effects and possible serotonin syndrome-like effects.(47-48)

*Severity ratings and comments based on information available in Natural Medicines Comprehensive Database (online; professional version).[11]

†The cytochrome P450 3A4 substrates most frequently involved in potential interactions with garlic were: amlodipine (n=16), atorvastatin (n=14), simvastatin (n=9), and verapamil (n=6).

[‡]The antidiabetes drugs involved in potential interactions with ginkgo biloba were: metformin (4), glyburide (2), and glipizide (1).

[††]The cytochrome P450 3A4 substrates most frequently involved in potential interactions with St. Johns Wort were: fluticasone (n=2), medroxyprogesterone (n=2), and trazodone (n=2).

[‡‡]The ACE Inhibitors involved in potential interactions with cayenne pepper were: lisinopril (6), benazepril (n=2), and enalapril (n=2).

Table 5

Odds of Exposure to a Potential Medication-Herb/Natural Product Interaction Among Participants Using at Least One Herb/Natural Product and at Least One Prescription or Over-The-Counter Medication

Characteristics	Odds Ratio (95% CI)	p	Adjusted Odds Ratio† (95% CI)	p
Female	1.03 (0.58-1.82)	.92	1.00 (0.53-1.92)	.99
African-American	1.43 (0.85-2.40)	.18	1.55 (0.86-2.78)	.15
Age, years	1.02 (0.99-1.04)	0.14	1.03 (1.00-1.06)	.06
Some College	1.09 (0.67-1.78)	.73	1.08 (0.61-1.91)	.80
Original Cohort	1.58 (0.96-2.61)	0.08	1.77 (0.99-3.16)	.06
Health Insurance	0.31 (0.14-0.69)	.004	0.34 (0.13-0.89)	.03
Disability Score	1.22 (0.88-1.69)	.24	0.61 (0.38-0.97)	.04
Depression Score	1.02 (1.00-1.04)	.10	1.01 (0.98-1.04)	.44
Fatigue Score	1.01 (1.00-1.02)	.004	1.00 (1.00-1.02)	.11
# of Comorbidities	1.44 (1.19-1.74)	.0002	1.27 (0.99-1.61)	.06
# of Herbs Used	1.31 (1.13-1.51)	.0002	1.29 (1.10-1.51)	.001
# of OTC Medications Used	1.32 (1.04-1.67)	.03	1.44 (1.09-1.91)	.01
# of Prescription Medications Used	1.14 (1.06-1.24)	.0005	1.13 (1.02-1.26)	0.02

† Due to missing data, N=419 in the logistic regression model.