Public Health Nutrition: 3(4A), 453–457

Epidemiologic challenges in the study of the efficacy and safety of medicinal herbs

Lenore Arab*
Departments of Nutrition and Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA

Abstract

Although clinical trials are needed to prove the efficacy of medicinal herbs and pharmacological studies are essential to the long-term goal of identifying the active ingredients in plants, these will not be forthcoming rapidly enough to meet the acute public health needs for knowledge on efficacy and safety since these substances are currently being widely consumed at various dosages. Resulting from the ongoing 'natural experiment' well-conducted observational epidemiology can bridge the gap and determine whether, as consumed its use is of benefit or detrimental, for whom and when in the course of disease prevention or minimization of disease severity. The classic study designs (cohort and case-control) and the more recent development of case-only studies can be put to service for these purposes. The challenges are in dose assessment, understanding mechanisms of effect, determining the relevant time period of exposure for a given disease or symptom, controlling for confounding factors such as disease status, and the special challenges presented by irregular use of medicinal herbs and concurrent use of multiple products and multiple sources.

Keywords
Epidemiology
Medicinal herbs
Safety
Efficacy
Dose

A natural experiment of huge dimensions is underway in the United States. Millions of individuals are self-prescribing the use of biologically active agents for the preservation of their health. Whether these products are effective, a waste of money, or actually causing damage remains largely unknown. The concept that these products are 'natural' and have been used for a long time is not adequate to insure safety or efficacy. It is true that the usage dates back to the earliest records of Mesopotamia from the time of Hammurabi, in Egypt as documented in the Ebers Papyrus (16th Century BC), and later in Greece and Rome at the time of Christ. Arab medicine was largely responsible for the preparation of pharmaceutics through evaporation, filtration and distillation of vegetables, herbs and the production of pills, syrups and essences[1]. India, Asian countries and Native Americans also have histories rich in the development and application of medicinal herbs. This long term use as often resulted in assumptions of these products being safe either because of their histories or because they are of natural origin[2]. The same could be argued for plants such as tobacco and comfrey, both now of known toxicity.

Many of the challenges to the scientific acceptance of medicinal herbs were experienced and documented in the 15th Century, when Aureolus Theophrastus Bombastus von Hohenheim (a.k.a. Paracelsus) proposed putting chemistry to the service of medicine (iastrochemistry). He was the municipal medical officer in Basle, Switzerland and was forced to leave this position because of disputes with the authorities. He is described in Stedman's Medical Dictionary[3] as someone whose 'teachings were a strange mixture of conceit, showmanship, senseless bombast, mysticism, astrology and sound medical wisdom', a description that suits as well the many attitudes in our society currently about forms of alternative medicine.

The acceptance of herb based therapies should come with rigorous scientific proof of safety and reasonable establishment of efficacy. The true proof of the effectiveness of a medicinal herb consumed in a given form at a given frequency and dose is traditionally established by clinical trial. For a number of reasons, clinical trials on the range of products being used, at the various doses being employed, in various populations of healthy individuals and those with specific diseases or vulnerabilities will not be available for a long time to come, if at all[4]. Until such clinical evidence is available, observational epidemiologic research is needed to capture the messages to be learned from this natural ongoing population experiment, to reinforce use where a benefit is found, and to spread the knowledge of risks that may be incurred with the use of individual preparations or combinations at specific doses.

With this argument, this article is based on four theses:

1. Clinical Trials are needed to prove the efficacy of medicinal herbs.

Corresponding author: Email LenoreA@unc.edu

https://doi.org/10.1017/S1368980000000537 Published online by Cambridge University Press

2. Pharmacologic studies are essential to the long-term goal of identifying the active ingredients in plants.
3. These will not be forthcoming rapidly enough to meet the acute public health needs for knowledge on efficacy and safety since these substances are currently being widely consumed at various dosages.
4. Resulting from the ongoing 'natural experiment' well-conducted observational epidemiology can bridge the gap and determine whether, as consumed its use is of benefit or detrimental, for whom and when in the course of disease prevention or minimization of disease severity.

In a recent paper in the *Journal of the American Medical Association* entitled 'Problems with Natural Products'[5] the primary problems with the use of medicinal herbs are presented as being the lack of data on adverse effects, the need for knowledge on drug-herb interactions, the lack of evidence of efficacy, the absence of information on active constituents (pharmacology), the variation between and within products, and the lack of monitoring of deterioration, contamination and adulteration. Well-conducted and well-designed epidemiologic research can help overcome the knowledge deficits implicit in these concerns.

Epidemiologic challenges

The study of current use of medicinal herbs in populations presents many challenges. They include the difficulty in assessing the dose taken, the factors such as health status, education, life style, and symptoms which influence and may bias the use of medicinal herbs, and the increasingly diverse variety of products through which these herbs are available, including various foods and beverages to which these have been added.

The analysis of effects of medicinal herbs needs also to consider the concurrent use of multiple products, fluctuations in use, seasonality of symptoms, and the confounding factors that could lead to a misinterpretation of effect.

A number of arguments have been employed to debate the how useful observational epidemiology (also called non-experimental epidemiology) is as a means of eliminating our knowledge deficits, they are usually the following. Firstly, we need to know the active ingredients first, in order to understand what we are examining. Secondly, the dose, as it is not directly administered from a known and measured source, is an unknown entity and may differ greatly from the expected dose for the reported intakes. There may not even be active ingredients in the medicinal herb product. Thirdly, since usage fluctuates greatly from day to day and month to month, it is extremely difficult if not impossible to relate usage to a specific outcome. Fourthly, there is concern that the use of such products may be biased by health status or an indicator of lifestyle and therefore not directly associated with the outcome under study. This would be the case if either the worried well or those more severely ill are more likely to turn to medicinal herbs.

Knowledge of biologic mechanisms

The concern that one needs to understand the biologic mechanism to study efficacy has not proven to be true. In fact, there is strong evidence that epidemiology is most powerful and effective at rapidly identifying associations and interactions without knowledge of the underlying biological mechanisms or active ingredients. Many if not most of the memorable epidemiologic breakthroughs have been with unknown agents, as was the case with cholera, AIDS, EMS, and Toxic Shock Syndrome. In the case of cholera, the water supply was identified as the source of the infection at a time when there was no knowledge of micro-organisms and their mechanism of action. AIDS was identified as being associated with homosexual behaviours long before the viral origin was understood. The relationship between Toxic Shock Syndrome and tampon use or Legionnaire's disease and air conditioning exposures are two more examples of extremely important and preventive epidemiologic discoveries that prevented further disease without knowledge of the active agents.

Dose assessment

The counter-argument to the issue of unknown dose is that whatever the true dose may be, the currently used doses are the relevant doses. Even if they include zero or if some products are adulterated or contaminated, for example with preservatives or pesticides, if product use involves this exposures- we want to measure then and determine whether use of the product (whatever is in the packaging) is associated with risk or benefit. If the conclusion is that there is an effect, and no active ingredients can be identified- this might suggest a valuable placebo effect. If use were associated with risk, regardless of the discovery of this being caused by a contaminant- usage would be reduced in the interim and thereby the public health preserved.

Relevant time period of exposure

In addition to accurate dose-assessment, an even more significant issue characteristic of all chronic disease studies applies here as well, the determination of the relevant time frame for consumption. So, for example, if the outcome of interest is cancer prevention, the multi-stage nature of carcinogenesis makes estimation of the time or times during the course of the disease that herbal product use has potential for impacting disease etiology is particularly challenging. From nutritional epidemiology

we know that people are relatively consistent in their relative patterns of usage of many foods. Fish eaters for example tend to continue this behaviour lifelong, and those adverse to fish do not often change their attitudes and behaviours. This allows assessment of intake at any given point time period in their life to be used for relative ranking of individuals with regard to their history of use. This can not be assumed for medicinal herb use, which is a function of trends and availability of products in the marketplace at a given time and place. The resulting limitations for observational epidemiologic study can be addressed in observational epidemiologic studies through the use of repeated prospective assessment of use in a cohort design for diseases with long preclinical development. For shorter term effects of medicinal herbs, such as their effect on mood, allergic responses, inflammation, infections, pregnancy outcomes or acute symptoms (i.e. urinary flow rates), recent use can be assessed by recall of prior use in case-control and case-only designs.

Confounding factors

Concern about confounding factors – those associated both with the exposure of interest (herbal use) and the outcome of interest (disease prevention or symptom minimization) is central to the design and analyses of any and all epidemiologic studies. Age, gender, diet, alcohol use, and numerous other factors can be confounders and cause spurious conclusions if not appropriately handled. However, many strategies for handling measurable and measured confounders do exist for study analysis. In addition, confounding by disease status is a problem that can be addressed by the selection of a study design (such as a cohort) which begins prior to disease onset.

Irregularity of use

Unlike multiple vitamins, most medicinal herbs are not used daily over long periods of time. The patterns of use tend to be driven by a variety of factors including the popular press, season of year, individual perceptions of health, presence of symptoms, cost, and the presence of these substances in other foods. This complex pattern of use can be challenging to model and incorporate in dose-response studies of effect. If information on enough persons is available, with differing patterns of intake, this can be converted into daily averages, treated as frequencies of consumption and modelled as regular, sporadic and seasonal use. The concerns about lack of analytic methods that can account for changes in exposure are equally unwarranted. Economic models do exist that can be applied to the latter. Concern about the availability of larger numbers of individuals at various levels of the intake distribution needed to adequately characterize risk or efficacy at various exposure frequencies is likely to be a moot point when half of the population is using these products. The challenge lies in contacting and motivating individuals across the spectrum to participate and reliably report their consumption patterns. This is the basis of all epidemiologic studies. Even if this level of quantification were not possible, chronic disease epidemiology relating disease risk without refinement of long term exposure has proven that even qualitative findings can be of great value.

Epidemiologic strengths

For most medicinal herbs, there is limited evidence from well-regulated experiments or trials regarding the biologic effects for which they are promoted. Even where evidence of a biologic effect has been demonstrated consistently in animal models or in vitro, this does not insure an effect in man. Epidemiologic results are needed to confirm whether animal and in vitro study findings translate into in vivo effects of medicinal herb consumption in man at the doses consumed, in the forms consumed and in light of the coexistent diet of the population. If no effect can be detected in a well designed epidemiologic study with adequate power to detect the effect; either the doses consumed are not effective in the context of the rest of the lifestyle, diet and environment of the population.

Epidemiologic studies are designed and analyzed to minimize bias and confounding and to allow external generalizability of the findings. Much of what is currently propagated about medicinal herbs is based on the belief that natural means safe[1] and on case study reports, which are similar to the narratives passed on from individual to individual about effects of these products. It should be noted that case studies are not epidemiology. With the number of subjects equaling one, the epidemiologic principles and procedures that minimize selection bias, control for confounding and allow for external generalizability are not enforceable. There is no hypothesis testing in a case report, and no ability to control for confounders. These reports are similar in this way to the limitations of ecologic studies, but are of less value since there is no variance in exposure, and no ability to examine probabilities of an outcome or its avoidance.

There are a number of different epidemiologic study designs that can bridge the gaps in our knowledge. They include cohort studies, case control studies and case only studies. The advantages of epidemiologic cohort study of medicinal herb use include the ability to study multiple outcomes, both short term and longer, and the ability to closely quantify patterns of use over time. As with other exposures, cohort study designs also eliminate any risk of recall bias in the reporting of prior exposures. So, for example, one could envision a study of breast cancer survivors, monitor their self selected use of medicinal herbs and follow up a variety of outcomes, ranging from quality of life to survival. A large advantage of this over a

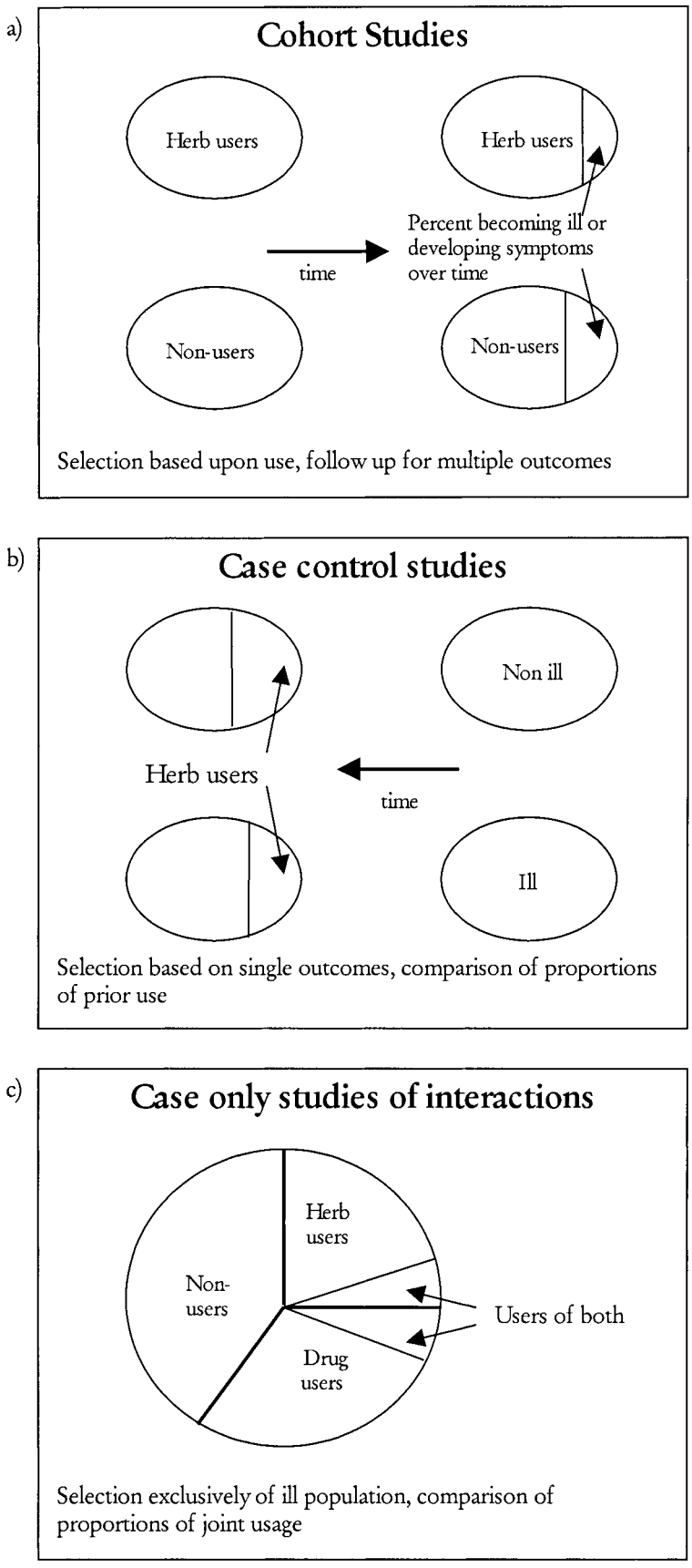

Fig. 1. Observational epidemiology study designs for the effect of medicinal herbs usage.

https://doi.org/10.1017/S1368980000000537 Published online by Cambridge University Press

clinical trial is the range of dosage that individuals select, which is likely to exceed that which might be allowed in a clinical trial, and the ability to study a wider dosage range than a single trial would permit.

Case-control studies, which can be equally valid if well designed, have other advantages, including much more rapid results and lower costs. They differ in their point of departure, with selection of subjects based on the presence or absence of an outcome, not the presence or absence of the medicinal herb use. From there, the proportion of users in the outcome groups are compared, and used to estimate the relative risk of that outcome as a function of medicinal herb usage.

A third study design, which is relatively new to epidemiology and very effective for the study of interactions is the case-only design[6,7]. In this design, individuals with a disease are selected, and differences in proportions of dual exposures, as for example the magnitude of the association between medicinal herb use and use of another pharmacologic product on a particle disease or side-effect outcome. This method will detect departures from multiplicative relationships between the two exposures. There is one caveat to the application of the case-only method. It is critical that the use of both herbs and the medication are independent of one another for this approach to provide valid results. For the non-epidemiologist, the differences in design between cohort, case-control and case-only studies are presented in Fig. 1(a–c).

Conclusion

In conclusion, the current status of our knowledge of the efficacy and safety of medicinal herbs, as evidenced by the excellent reviews in the monograph, is grossly inadequate. There is very little epidemiologic data; there are very few clinical trials on these substances and almost nothing on interactions. The use of medicinal herbs by humans to prevent or control disease in the United States represents a natural ongoing experiment, which has begun and is ideally suited for study with epidemiologic methodology. Both well designed cohort and case-control studies can make significant contributions to the immediate need for evaluation of efficacy and safety of the products currently being sold and consumed by the population.

To return to Paracelsus, his basis tenet was 'the dose determines the poison'. Any biologically active substance consumed in excess carries a health risk. The challenge is to determine if there is a risk at the doses consumed by the population, in addition to determining whether use at all carries any benefit other than the stimulation of the economy being noted by this rapidly growing billion dollar business.

Well designed epidemiologic studies of medicinal herb use within the population, controlled for confounders, will provide evidence of a beneficial or harmful effect of use of the products currently available in the self-prescribed dosages that are being taken. A number of challenges remain, including quantitation of effect, determination of active ingredients, and the additive use of multiple and changing products.

References

1 Mez-Mangold L. A History of Drugs, Editiones Roche, Basel, 1971.
2 Arab L. Medicinal Herbs: Naturally Safe? *Public Health Nutrition* 2000; **3**: 111.
3 Stedman's medical dictionary. 23rd edn Baltimore: Williams & Wilkins; 1976.
4 Block G, Patterson B, Subar A. Fruit, vegetables, and cancer prevention. A review of the epidemiological evidence. *Nutr. & Ca.* 1992; **18**: 1–29.
5 Eisenberg DM, Kaptchuk TJ. The herbal history of digitalis: Lessons for alternative medicine – Reply. *JAMA-Journal of the American Medical Association*. **283**: (7) 885–886 Feb 16 2000.
6 Begg CB, Zhang ZF. Statistical analysis of molecular epidemiology studies employing case-series. *Cancer Epidemiol Biomarkers Prev*. 1994; **3**: 173–175.
7 Piegorsch WW, Weinberg CR, Taylor JA. Non-hierarchical logistic models and case-only designs for assessing susceptibility in population-based case-control studies. *Stat. Med.* 1994; **13**: 153–162.