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Ethical considerations in clinical research on herbal medicine for prevention of cardiovascular disease in the ageing

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ABSTRACT

Background: Cardiovascular disease (CVD) in the ageing is a major public health problem worldwide. The nature of most CVD is subclinical with pathological processes that can span over years. Use of preventive measures could be an appropriate approach to prevailing over CVD in the ageing, and herbal medicine is one of the promising preventive approaches and is currently of interest among medical societies. In the evidence-based era, herbal medicine is, however, often underestimated and approached with skepticism, mainly due to the paucity of scientific evidence. Properly designed clinical trials on herbal medicine for prevention of CVD in a geriatric population are thus of importance and of clinical value.
Purpose: To review ethical issues and discuss considerations when such research is proposed.
Chapters/sections : Four ethical issues, including the scientific validity of research, risk-benefit assessments, subject selection and vulnerability, and informed consent, are structured and extensively discussed in this article.
Conclusions: Ethical core considerations of prevention research of CVD on herbal medicine involve particular attention on the scientific validity of research, risk-benefit assessments, subject selection and vulnerability, and informed consent. These issues and considerations are keys, although they must be adapted to an individual research setting in which a clinical study is proposed.

Introduction

Cardiovascular disease (CVD), a class of diseases involving the heart and blood vessels, is one of the leading causes of death and disability worldwide (Fuster 2014; Global Burden of Disease Study 2013 Collaborators 2015). In the US, an estimated 10%, 40%, 70%, 85% of population with 20–39, 40–59, 60–79, and > 80 years of age respectively have at least one form of CVD, reflecting a marked increase in the incidence and prevalence of CVD in correlation with advancing age (Mozaffarian et al. 2015; Yazdanyar and Newman 2009). Most cases of CVD in the ageing have the hidden progression of pathological processes that may take years or decades before development of clinical manifestations. Use of preventive medicine during this time lapse could prevent the occurrence (primary prevention), progression (secondary prevention), and/or complications (tertiary prevention) of CVD in an individual, who is considered healthy currently (Clarke 1974; Taylor et al. 2013; Van Horn et al. 2008). Continuous management of subclinical pathology through the concept of preventive medicine, in other words suppression or prolongation of asymptomatic pathological processes, requires very safe agents that to be regularly taken for an individual's lifetime. Use of phytomedicine in the elderly population for the purpose of preventing CVD is thus of interest (Luo et al. 2013).

Phytomedicine, also called herbal medicine, refers to the preparation of plants or parts of plants for medicinal purposes. It is of interest among populations worldwide for its use in primary health care and management of conditions, including CVD (Grant et al. 2012; Li et al. 2015; Tachjian et al. 2010). A recent trend in the use of herbal medicine and/or other natural products globally is partly due to the increasing preference for natural therapies and/or preventive medicine, rising concerns about the undesirable side effects of Western medicine, and the spreading belief that natural products are safer (Calixto 2000; Zhang et al. 2015). Despite the widespread use of herbs in traditional medicine for centuries, phytomedicine is often underestimated and approached with skepticism, mainly due to the paucity of scientific evidence (AnthonyLin et al. 2011; Fung and Linn 2015). Standard research with modern scientific approaches on many herbal

Abbreviations: CVD, cardiovascular disease; EMEA, European medicines agency; HPLC, high-performance liquid chromatography; ICF, informed consent form; LAR, legally acceptable representative; SDM, surrogate decision maker.

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medicinal products has just started in recent years. Evidence-based efficacy and safety of herbal preparations in the ageing with CVD has been formulated but still limited at this moment in time (Cohen and Ernst 2010; Frishman et al. 2009; Fugh-Berman 2000; Li et al. 2015; Sham et al. 2014; Tachjian et al. 2010; Valli and Giardina 2002).

To fill the niche of effective and pathogenetically-targeted pretreatment and treatment of hidden cardiovascular pathologies, which can eventually result in other life-threatening diseases, properly designed clinical trials on herbal medicine for prevention of CVD in geriatric populations are warranted. Here, we review and discuss ethical issues related to clinical research on herbal medicine as preventive measure for CVD in the ageing.

Ethical considerations

In general, any clinical research in product development, including herbal drugs, must be subjected to the same ethical standards in accordance with international and national ethics guidelines and regulations. Research design and the conduct of research must be ethically sound. Ethical issues must be identified, extensively discussed and properly addressed in an ethically acceptable manner. Particularly in regards to the nature and perception of herbal drugs, prevention research of CVD, and the conduct of research in ageing populations, four main ethical issues are identified and extensively discussed in this article.

Scientific validity of research

Clinical research in which the design or methodology itself is unlikely to produce scientifically reliable or valid results is *ipso facto* unethical in that it may place research participants at risk and worse for no purpose (CIOMS 2002; Emanuel et al. 2000). Scientific validity is therefore an essential element that makes research ethical (Emanuel et al. 2000).

Active compound(s) and quality control of the study drug

Compared to synthetic agents, common practical challenges of evidence-based approach in herbal medicinal products are: (1) unknown active compound(s) or the complexity of compounds that contributes to pharmacological activities of the whole product and (2) absent or insufficient quality control and standardization of the product (Harkey et al. 2001; Valli and Giardina 2002). The complexity of synergistic, additive, or antagonistic pharmacological effects of many constituents in herbal products complicates the identification of responsible compounds for each pharmacological activity of the whole product (Wang et al. 2014). In addition, there are many factors, including intrinsic factors (*e.g.*, species differences, organ specificity, diurnal and seasonal variations) and extrinsic factors (*e.g.*, environmental conditions, cultivation and field collection practices, postharvest handling storage, contamination and adulteration), that often affect product-to-product or batch-to-batch variations of herbal products (AnthonyLin et al. 2011). Therefore, the conduct of clinical research on herbal medicine frequently raises concern on the reproducibility and reliability of the findings. Lack of quality control and product standardization could disqualify the research on the basis of limited scientific validity and also result in inapt risk-benefit assessments. Standardization and quality control of herbal medicinal products are not easy, but feasible. Establishment of a chemical fingerprint of a herbal product using high-performance liquid chromatography (HPLC), for example, could be applied (Fung and Linn 2015). The profiles of constituents in different batches can then be compared so that the reproducibility and generalization of the findings would be possible as a result. Following international guidelines and regulations on quality and information needed to support clinical studies of herbal products (*e.g.,* FDA guidance for industry (2004) on botanical drug products, Operational guidance (2005) on information needed to support clinical trials of herbal products, WHO guideline on good manufacturing practices for herbal medicines (2007), and EMEA guideline on quality of herbal and traditional medicinal products (2011)) could be worthwhile.

Study design and justification of a placebo-controlled design

The scientific value of a clinical study is partly attributable to the study design. However, a study design with only scientific integrity, disregarding ethical concerns, may turn the study into a social outcry as seen in gene therapy studies (Kimmelman 2008; Raper et al. 2003). In clinical research, randomization, blinding, and use of control group are technical means to minimize bias. A randomized placebo-controlled trial is considered as the gold standard for clinical research (Besen and Gan 2014; Karbwang and Na-Bangchang 2013). However, a randomized placebo-controlled design may not be applicable, appropriate or ethically acceptable in some circumstances. In herbal medicine research, the standardized treatment approach through a randomized controlled design may challenge a prominent concept of the individualized treatment approach or holistic therapeutic milieu in traditional medicine (Fung and Linn 2015; Miller et al. 2004; Tilburt and Kaptchuk 2008). In addition, to make an indistinguishable placebo for the herbal product under investigation, especially in the form of decoction, can sometimes be a challenge (Fung and Linn 2015).

Given the assumption that placebo is technically feasible, ethical consideration of the justification for using placebo in the context of an individual research study is necessary. In general, use of placebo may be ethically justified in research where there is no established effective intervention for a specific target group; however, when an effective proven intervention for a specific condition is available, use of placebo may be considered unethical (CIOMS 2002). Given the scenario of prevention research of CVD, it could be simply concluded that the choice of the comparator (placebo or active control) depends primarily on the availability of an established preventive therapy for a specific condition under investigation (ICH E10 2001).

However, additional consideration may be necessary with some conditions where a standard therapy is available. For instance, in a condition with an anticipated high placebo-response rate or spontaneous remission of symptoms in nature (*e.g.*, chronic stable angina), a clinical trial without a placebo arm may lead to a false or invalid conclusion, or a failure to determine the actual effect of the drug under investigation. Although the use of placebo in a trial involving patients under such a condition often raises ethical concern, it could be ethically sound under stringent criteria: (1) there is compelling methodological reasons for the use of placebo, (2) there is no serious or irreversible harm due to the use of placebo (in consideration of inclusion, exclusion, and withdrawal criteria), (3) there are adequate monitoring procedures and additional safeguards, and (4) there is a clear disclosure of the rationale for using placebo in an informed consent process (Amdur and Biddle 2001; Emanuel and Miller 2001; Miller et al. 2004).

Given the scenario of another condition where well-established interventions that can prevent a subsequent severe CVD exist (*e.g.*, hypertension or dyslipidemia), the use of placebo may not be ethically justifiable. This is based on the assumption that it would be unfair to research subjects who are assigned to receive no intervention despite the existence of an effective intervention. Withholding an established effective intervention (*e.g.*, an antihypertensive or antidyslipidemia agent) for certain periods of time, due to the nature of prevention research, would possibly expose subjects to serious harm or discomfort. However, clinical improvement of such a condition (*e.g.*, hypertension) could be attributed to not only the drug under investigation but also other medical care (Preston et al. 2000). Without a placebo arm, the findings of a non-inferiority trial with no difference between the investigational and standard treatment could thus be misleading or uninterpretable. A placebo-controlled study on top