

Invited commentary

The efficacy and safety of Chinese herbal medicines

The uses and practice of traditional Chinese medicines (TCM) date back centuries and are steeped in customs that encompass ancestral beliefs (concerning health), drug lore and “an understanding of natural laws” (Hesketh & Zhu, 1997; Unschuld, 1999). Today TCM (on its own or in conjunction with conventional medicine) is an integral component of healthcare systems in the Far East and is used to treat disease and to promote health and wellbeing (Hesketh & Zhu, 1997; Scheid, 2000; Bodeker, 2001; Wang & Ren, 2002).

Over the past decade, Western medicine has witnessed the keen embracing of certain elements of TCM, especially Chinese herbal medicines (CHM) and their commercial derivatives. These medicines are said to possess numerous properties and as a consequence are used to treat a variety of diseases including arthritis, cancer, asthma and allergies (Brooks & Lowenthal, 1977; But & Chang, 1996; Chan & Critchley, 1996). *Ganoderma lucidum*, or ‘Lingzhi’, the focus of the paper by Wachtel-Galor *et al.* (2004b) in this issue of the *British Journal of Nutrition* is a prime example of the multifarious nature of CHM. *G. lucidum* is a very popular Chinese medicinal fungus, which has long been used as a sedative. It is reported to possess anti-tumour, anti-hepatotoxic, antinociceptive and immunomodulatory properties and has been used in the treatment of hypercholesterolaemia and hypertension (Jong & Birmingham, 1992; Lin *et al.* 1995; Koyama *et al.* 1997; Wang *et al.* 1997, 2002; Wasser & Weis, 1999; Bao *et al.* 2001a,b; Liu *et al.* 2002). Moreover, the immunomodulatory properties of *G. lucidum* have been exploited in the development of possible treatments for both allergic asthma and food allergy (Li *et al.* 2000, 2001). *G. lucidum* is also used as a dietary supplement and health food (Chiu *et al.* 2000).

With the increasing use of CHM, such as *G. lucidum*, come the questions concerning their safety, regulation, efficacy and mode of action (Chan *et al.* 1993; Chan & Critchley, 1996; Tang *et al.* 1999; Ernst, 2000, 2003; Fugh-Berman, 2000; Mills, 2001). The use of CHM has been connected to a number of adverse effects resulting in nephropathy, acute hepatitis, coma and fever. In addition, neurological, cardiovascular and gastrointestinal problems have also been associated with CHM (Chan *et al.* 1993; Vanherweghem *et al.* 1993; Chan & Critchley, 1996; Lord *et al.* 1999; Nortier *et al.* 2000; Park *et al.* 2001). Cases of poisoning have been linked to variations in the chemical composition of different brands of the same herb. Such differences may arise as a result of inadequate processing (processing normally involves soaking and boiling the raw material) resulting in toxins being retained, and adulteration with cheaper substitutes (Chan & Critchley, 1996; Fugh-Berman, 2000; Li & Sampson,

2003). (Adulteration may also obscure the true benefits of CHM as well as contribute to them (Keane *et al.* 1999).) Cases of poisoning may also be attributed to heavy metals (Cd, Pb, Tl and Hg) present in both unprocessed CHM and their commercial derivatives (Wong *et al.* 1993; Chan & Critchley, 1996; Chiu *et al.* 2000).

The misclassification of species and the mistaken substitution of Chinese herbs have also given rise to serious adverse affects (Chan *et al.* 1993; Vanherweghem *et al.* 1993; But, 1994; Chan & Critchley, 1996; Fugh-Berman, 2000). For example, a product believed to contain ‘Siberian ginseng’ but on analysis was shown to contain Chinese Silk Vine, has been linked to a case of neonatal androgenisation in North America (Koren *et al.* 1990; Awang, 1991). Misidentification of CHM can also lead to erroneous explanations concerning their mode of action. In correspondence concerning the anti-allergic properties of the CHM ‘Food Allergy Herbal Formula-1’ (FAHF-1), the incorrect identification of the chemical structure of one of its components (*G. lucidum*) led to ‘misleading conclusions’ about the causes of FAHF-1’s immunomodulatory action (Li *et al.* 2001; Claman, 2002; Towers, 2003; Li & Sampson, 2003). Concerns about CHM have been further reinforced by the potential for their interactions with conventional medicines causing effects that may ultimately result in modifications to the action(s) of the conventional medicines (Chan & Critchley, 1996; Chen *et al.* 2002; Fugh-Berman, 2000). An example of such an interaction is that of warfarin and *Angelica sinensis* (dong quai) or *Salvia miltiorrhiza* (danshen). Evidence suggests that the bioavailability and elimination rate of warfarin, plus platelet function, are affected by these CHM (Chan & Critchley, 1996; Fugh-Berman, 2000).

Clearly these issues highlight the need for further in-depth research on CHM and other herbal medicines. The National Center for Complementary and Alternative Medicine (NCCAM; <http://nccam.nih.gov>), a US Congress-funded body, actively supports research and development in the area of CHM. In addition, the Department of Complementary Therapies at Exeter University in the UK has highlighted the need to adhere to rigorous scientific methodology in the carrying out of research on CHM and other alternative and complementary therapies (www.ex.ac.uk/FACT).

In studies on CHM, a variety of approaches have been used. Some studies have focused on analysis, others on biological activities, safety, bioavailability and mode of action using either cell or animal models (Lin *et al.* 1995; Kawagishi *et al.* 1997; Chiu *et al.* 2000; Bao *et al.* 2001a,b; Chen *et al.* 2002; Wang *et al.* 2002; Xu *et al.* 2003). Many studies have used randomised controlled trials (RCT) to address the question of efficacy. A systematic

review of RCT of TCM highlighted issues concerning the quality of some of these studies, specifically methods of randomisation, the use of inappropriate controls, duration and expression of effectiveness (Tang *et al.* 1999). However, as pointed out by Ernst (2003), one should not assume that all RCT on the efficacy of alternative and complementary therapies are of 'inferior methodological quality' and well-designed RCT are in the literature (Ernst, 2001, 2003). Yet despite the presence of these rigorous RCT, in comparison with other areas of biomedical research, there is a paucity of data relating to the efficacy and safety of CHM (Ernst, 2003).

The study by Wachtel-Galor *et al.* (2004b) contributes to this relatively small library of knowledge on CHM. In their study the reported biological and beneficial effects of *G. lucidum* were investigated using an objective and controlled approach. A previous study by Wachtel-Galor *et al.* (2004a) on the effects of short-term (10 d) supplementation of *G. lucidum* (using biomarkers of antioxidant status and CHD risk) reported increased antioxidant levels and indicated that this CHM may reduce the risk of CHD. The present study has taken the investigation of *G. lucidum* further by studying its effects using additional biomarkers of function, namely inflammatory function and immune function; the toxicology of *G. lucidum* was also investigated by monitoring biomarkers of liver and renal toxicity and genotoxicity. The results of the study indicate that after a 4-week period of supplementation (using healthy subjects) plasma lipids were decreased (although this change was not statistically significant) and antioxidant levels in urine were increased. In addition, there was no evidence of hepatic and renal toxicity and genotoxicity. The latter finding, concerning genotoxicity, concurs with that of Chiu *et al.* (2000) in which nutritional and toxicological assessments of *G. lucidum* were carried out.

The study by Wachtel-Galor *et al.* (2004b) has identified areas that need to be pursued with regards to the efficacy of *G. lucidum*. The authors are currently planning to study further the putative lipid-lowering effect of this CHM and its components using at-risk subjects. In addition, the authors' hypothesis regarding *G. lucidum* (specifically its components and metabolites) working in conjunction with dietary and endogenous antioxidants, as part of a global system, could form the basis for a study that may provide some insight into the reported antioxidant action of this CHM. Moreover, speculation, made by the authors, about the possible impact of bioavailability on the efficacy of *G. lucidum*, indicates that the role of the gastrointestinal tract on *G. lucidum* requires further investigation. Exploration of these areas is essential to the furthering of our knowledge and understanding of the effects of *G. lucidum*. Furthermore, the strategies that are to be developed, so that rigorous study of these areas is achieved, will contribute to research and development in the area of CHM.

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