Methods to Ensure Microbiological Safety of Organically Produced Medicinal Plants: A Review

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Abstract. The production, handling, processing and marketing of over-the-counter medicinal products manufactured from plants is virtually unregulated. This can include dietary supplements, functional foods and nutraceuticals, any of which may contain botanical constituents. Of particular concern is the possible presence of human pathogens in products offered at retail. A review of literature is presented. Options for sterilizing herbal medicinal products, including fumigation, irradiation and heat treatments, are presented. Experiences of the spice industry are discussed as they relate to the development of similar protocols for herbal medicines. Methods used to ensure microbiological safety must be evaluated for their effect on the medicinally active constituents in the plant material. Very little data of this nature are available. Avenues for future research are proposed.

Safety of herbal medicines has been a concern since the commercialization of these products began decades ago (Farnsworth, 1993). Safety is best assured through the implementation of Good Agricultural Practices (GAP) and Good Manufacturing Practices (GMP), the concepts of which intuitively are clear. However, to define their meaning in the context of the safety and quality of herbal medicinal products is relatively complex. Key points were reviewed by Franz (1989) and Demarco et al. (1999) expanded the discussion relative to organic production. Increases in consumption of botanicals during the past two decades are forcing a transition from harvesting plants from their native habitat (wild-crafting) to large scale cultivation (Pank, 1993) and have called greater attention to GAP and GMP. Organic cultivation in particular calls attention to microbial safety. Franz (2004) continues to commit significant effort to GAP and GMP. Organic cultivation in particular calls attention to microbial safety. Franz (2004) continues to commit significant effort to GAP and GMP.

Early attention to herbal product safety focused on chemical residues. One approach was to establish safety coefficients for chemical use based on the rate of decay of the applied products (Debska and Lutowski, 1980). A notion that has been rejected in recognition of the fact that many chemicals persist in soils for extended periods and the potential exists for their uptake into plants (Grun et al., 1993).

Today we recognize that the safety and health properties of plant-based functional foods, medicines and nutraceuticals are far more complex than previously thought, encompassing issues of microbiological safety, allergens, dosage requirements, toxicity and product standardization. The need for standardization of botanical medicinal products is particularly compelling (Craker, 1999; Cranz, 1999; Lip- lipson, 1993). Implementation of GAP and GMP to help ensure product safety is a key prerequisite for standardization during production, harvesting, processing and marketing.

Experiences from the food industry are highly relevant to the herbal medicinal product industry. Food safety concerns led to the development of Hazard Analysis Critical Control Point (HACCP) programs, which have the purpose of ensuring food safety by focusing on all steps from harvest until consumption (USDA, 1998). The basis of HACCP is to identify hazards, defined as physical, chemical or microbiological in nature, and to impose controls upon critical steps to reduce risk to consumers. HACCP has served as a useful model for development of GAP and GMP, which go a step further to include all agricultural operations in addition to manufacturing.

In the food industry, the cases of fresh fruits, vegetables and spices are most relevant to the botanical medicinal industry. US-FDA (1998) published guidelines for reduction of microbial risks in fresh produce. This was treated more comprehensively by the Joint Institute for Food Safety and Applied Nutrition in a GAP-GMP training manual (JIFSAN, 2002).

An invaluable collection of resource materials for fresh produce is available from Cornell University (Bihn et al., 2004) and similar, but less comprehensive, documentation is available from the U.S. spice industry trade association (ASTA, 2003). Many of the guidelines and recommendations in these publications are directly applicable to herbal medicines.

Guidelines that specifically address botanicals are under discussion at U.S. Pharmacopeia (2003) and some published materials are available from international organizations (EMEA, 2002; WHO, 2003). In all of these resources, specific disinfection protocols are not discussed in a practical manner. No focused effort has been made to regulate the botanicals industry other than the publication of the Dietary Supplement Health and Education Act (US-FDA, 1994). Monographs for GAP and GMP for specific crops are needed. A limited amount of work has been published for feverfew (Tanacetum parthenium (L.) Shultz-Bip., Asteraceae) that could serve as a starting point for monograph development (Rushing et al., 2003). Canadian authorities also have published microbiological guidance for foods (Harwig et al., 1998) that are relevant to botanical medicinal products.

Spices and medicinal plant products often are investigated in parallel studies due to the similarities in production and postharvest practices. An example of this is found in the reporting of pesticide residues found in spices and medicinal plant products (Abou-Arab and Abou Donia, 2001). Microbiological quality and safety of spices has been the focus of a number of surveys including those of retail markets in the U.S. (Schwab et al., 1982), in India (Banerjee and Sarker, 2003), and in heavily spiced ethnic foods (Candlish et al., 2001). Enumeration of microorganisms in spices and spice mixtures has been an important activity in this industry for decades (Krishnaswamy, 1971), with periodic updates that recognize the risk of fecal contaminants (Satchell, 1989). A relatively recent review of this body of literature is available (McKee, 1995). Clearly the spice industry recognizes that food safety hazards exist in spices. The need to define acceptable microbial limits for herbs is acknowledged but such limits are not clearly defined (EMEA, 2001).

Imported medicinal herbs have been found, in some cases, to contain microbial contamination. In a survey of St. John’s wort [Hypericum perforatum (L.) Hypericaceae] imported from China, U.S. Pharmacopeia (USP) observed that, before irradiation treatment, a number of samples tested contained E. coli 0157, likely caused by the use of animal manures or human waste (night soil) during production (unpublished, personal communication with USP).

Irradiation would eliminate this hazard and this emphasizes the need to include a disinfection step in the processing of medicinal plant products. There is an understandable reluctance in the scientific community to publish such results without exhaustive confirmation because of the impact it might have on the industry in addition to possible liability issues.
Discussions with cottage-scale producers and vendors of herbs and with herbal medicine practitioners have revealed concerns for consumer safety. Methods for disinfecting small lots of fresh herbal products are needed. Some small-scale growers use un-composted organic fertilizers to produce herbs that are delivered to retail markets in a freshly harvested state, without further treatment. The risk of developing illness may exist for consumers that use these products without implementing a kill step, such as in the preparation of teas with boiling water (personal communications with conference attendees; see Rushing et al., 2003). It is useful to review the options available for sanitizing treatments of medicinal plant materials, recognizing that many potential treatments described herein are not certified organic.

IRRADIATION

Gamma irradiation. Gamma irradiation and ethylene oxide, discussed later as a fumigant, are used by some to be the industry standard methods for disinfection of herbs, spices and medicinal plant products (ASTA, 2003; Giddings, 1984; Mueller, 1998). Similar work with the irradiation of fresh fruits and vegetables is ongoing (Prakask, 2004). With any method of treating foods and nutraceuticals, whether the treatment is new or well-established, there are concerns for consumer acceptance. Surveys of consumer attitudes toward irradiated products consistently find that pesticides, not irradiation, are the primary consumer concern for safety (Bruhn, 2004; Eustice, 2004; Johnson et al., 2004). Since herbal medicinal products are not considered foods and workers concluded that gamma irradiation effectively killed microbes without damaging quality and safety is needed as a prerequisite for any regulatory measure.

The influence of gamma irradiation treatments on various quality factors in foods has been reported. The sensory, microbiological and nutritional quality of cilantro [Coriandrum sativum (L.) Umbelliferae], which may be considered a high risk herb, was investigated and workers concluded that gamma irradiation effectively killed microbes without damaging quality (Fan et al., 2003). In further studies, cilantro washed with chlorinated water prior to irradiation also had high consumer quality and was determined to be safe for consumption (Foley et al., 2004). Gamma irradiation was not found to impact the content of free radicals and antioxidants in selected herbs and spices (Calucci et al., 2003). In other work with the toxicological safety of irradiated foods, it was suggested that genetic modifications following irradiation are insignificant and should not be a consumer concern (Sommers, 2004). Gamma irradiation is used in the herbal medicinal industry to treat fairly large lots (e.g., 50 kg) with the assumption that penetration to the center of such amounts is adequate. Unpublished work regarding the presence of human pathogens in irradiated products available at retail suggests that this may not be true and that additional studies are justified. Spice extracts can modify efficacy of irradiation treatments (Sharma et al., 2000), suggesting that specific studies are needed for every specific crop or product.

Electron beam. Insufficient penetration of dense products, such as fruits and vegetables, is reported to be a limitation for electron beam (e-beam) irradiation treatment (Hallman, 2004), thus methods to facilitate penetration must be considered in order for e-beam to effectively disinfect any item. A further concern is the impact of e-beam irradiation on bioactive constituents in the irradiated product. A number of foods are under investigation (Patil, 2004) but reports of e-beam use for sterilization of herbal medicinal products and its effect on microbiological and medicinal quality are unavailable.

Ultraviolet light. Ultraviolet irradiation has practically no penetrating ability, e.g., its capacity as a disinfection treatment is strictly a surface effect (Fonseca, 2000). Partial inactivation of microbial contamination could be anticipated but it seems doubtful that complete sterilization could be accomplished. Ultrasonic and radio waves. Although the use of sound waves cannot be defined as irradiation per se, references to these technologies are often found in the same general body of literature. Ultrasonic has been tested and found suitable for the inactivation of Listeria monocytogenes in apple cider (Baumann et al., 2004). Radio frequency has been tested for sterilization of scrambled eggs (Luechapatnamorn et al., 2004) and as a quarantine treatment for cooling moth in fresh market apples (Hansen et al., 2004). Input of energy, including sound waves, into tissue results in some degree of heating, so isolation of the sound effect from heating may be a challenge for researchers.

FUMIGATION

Ethylene oxide. Ethylene oxide is registered for use as a sanitizer for spices and seasonings (USCFR, 2004; USEPA, 2004b) and its use is recommended by the spice industry in the U.S. (ASTA, 2003). Residues in products following treatment are a concern and its use has been banned in Europe and Australia for this reason (Richardson and Jackson, 2004; Steinhoff, 2003; Wilkes, 1992). Methods have been developed for testing ethylene oxide residues in fumigated products by head space analysis (Woodrow, 1995). Direct comparison of ethylene oxide fumigation to irradiation treatments has been reported for selected herbs and spices and generally, fumigation is less effective than irradiation for reducing microbial load (Marcotte, 2004).

Propylene oxide. Propylene oxide is registered for use as a fumigant for foods (USCFR, 1998). Beuchat (1973) investigated its use for reducing the load of E. coli 0157:H7 on fresh shelled pecans and more recently it has been utilized for control of Salmonella enteriditis phase type (PT) 30 in almonds (Danyluk et al., 2005). The current body of literature for botanical medicine makes little or no reference to propylene oxide.

Chlorine dioxide. Chlorine dioxide is an extremely effective biocide (USEPA, 2004a). A review is available from Simpson, et. al. (2004). Lee, et. al. (2004) reported that chlorine dioxide fumigation of lettuce leaves controlled microbial pathogens without damaging the quality of the product. Other studies address the microbial safety and quality of mushrooms following fumigation (Selby et al., 2004) and its use for decay control in apples (Lee and Kang, 2004).

Ozone. Reports are lacking on the treatment of medicinal plant products with ozone, but the database from other industries is extensive. Ozone technology is used in the dairy industry for sanitizing facilities such as storerooms and for water treatment (Yuan, 2004). An advantage of ozone for plant materials is that it degraded pesticide residues on fruits more effectively than chlorine treatment (Liu and Ruan, 2004). The use of ozone as a sanitizer in fresh produce handling systems has been reviewed (Smilanick et al., 1999).

Phosphine. Phosphine gas, often referred to as phostoxin, is widely used for the fumigation of medicinal herbs (personal communication, Mr. Edward Fletcher, Strategic Sourcing, Inc., Banner Elk, N.C.). The label allows for its use as a pest control in raw agricultural commodities (USEPA, 2005), but reports on its efficacy for control of microorganisms are not available.

Other fumigants. Sulfur dioxide (Luvisi et al., 1992), methyl bromide, ammonia, and probably other gaseous fumigants have activity against microorganisms. Any of these might potentially leave undesirable by-products in herbal medicinal products. Aug (2004) is currently investigating methyl bromide and possible alternatives for maintaining post-harvest quality of fresh produce, but similar studies for herbal medicinal products are not available.

HEAT

Rushing et al. (2004) reported on the effects of temperature during drying on the quality of feverfew herb. Adequate air movement through the product is essential for the prevention of growth of mold. Dryers that are fueled by petroleum gas should be equipped with heat exchangers to avoid the possible formation of nitrosamines in plant tissues (Hecht, 1998). Steam heat has been suggested as an alternative to ethylene oxide fumigation for disinfection of herbs and spices (Richardson and Jackson, 2004; Wilkes, 1992). Clearly a drying step must follow the application of steam heat. The influence of microwave heating on herbal medicinal products has not been reported.

FUTURE WORK

A logical starting point is simply to define the scope of microbiological contamination that may exist in commercial herbal medicinal products. This would provide the justification
for further work and establish a baseline for research with sanitizing protocols. A number of microbiological testing methods are available that are relatively quick and easy to use. Comparisons of various methods have been reported (Cundell, 2002; McIntyre, 2004). For initial studies, samples could be tested for aerobic plate counts and total coliforms according to the methods defined by U.S. Pharmacopeia (2005). Additional tests should be employed as the need is justified. Direct comparison of the microbial load found on organically produced herbs to those produced with conventional methods is needed. Variables such as the source of organic material, composting methods, and time lapse from the application of organic matter to harvest all are issues of concern.

Of special interest to the industry are postharvest treatments, specifically sanitizing treatments that eliminate the risks presented by viable microbial pathogens. Variables in sanitizing treatments, e.g. time, temperature, etc. that impact efficacy should be investigated as well. Attention to costs vs. benefits is a key industry concern.

Also of concern is the impact of sanitiz- ing treatments on the medicinal quality of the plant or its processed product. Microbiological studies should be complemented by appropriate biochemical analyses to determine if the medicinally active component is degraded by the sanitizing treatment. The author has work of this nature in progress utilizing feverfew as a model system (Rushing, 2005). Parthenolide, a sesquiterpene lactone, has been analyzed in previous studies as an indicator of feverfew medicinal quality (Fonseca, 2003; Rushing et al., 2004). The methods for parthenolide analysis described in those studies are utilized in the current work. Parthenolide in feverfew is being extracted and analyzed by high-performance liquid chromatography (Shimadzu LC-10AT) before and after sanitizing treatments. During the course of this work treatments will be developed to elucidate the optimum treatment methods for preserving feverfew quality, i.e. parthenolide content, while reducing the microbiological load.

CONCLUSION
Safety of medicinal herbal products is an abiding concern for consumers and for the industry as a whole. The emphasis on safety has been traditionally focused on potential chemical hazards which are relatively easy to analyze and control. Today there is increased attention to microbiological safety. The PI has addressed GAP and GMP for feverfew in previous studies (Rushing et al., 2003) and further work will identify the safety-quality relationships that exist within post-production handling systems (Rushing, 2005). Of special concern is the adherence to organic production practices and the microbiological risk associated with the use of manure and bio-solids as fertilizers. Sanitizing techniques that could apply equally well to both small-scale and large-scale producers and handlers of herbal medicinal crops and products are needed. Fulfillment of those needs will create opportunities for large- and small-scale growers and handlers to enter this relatively new market with confidence in their ability to provide safe herbal products of high quality.

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