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Review

Fermentation, a feasible strategy for enhancing bioactivity of herbal medicines

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ABSTRACT

Herbal drugs, which possess immunomodulatory, anti-inflammatory, anti-diabetic, anti-infective, and anti-allergic activities, encompass various therapeutic areas, and have been used as traditional medicines for thousands of years. Fermentation is an indispensable traditional technology for the improving the efficacy or reducing adverse effects of herbal medicines. The fermentation process has been shown to improve biological properties of plants, vegetables, and herbs. More specifically, fermentation causes decomposition and/or biotransformation of complex substrates into compatible components, thereby modulating product properties or changing the quantity of certain bioactive compounds. Accumulating evidence indicates the valuable contribution of probiotics and their fermented food products to health. In recent years, considerable attention has been paid to fermentation technology across the globe for improving herbal drugs through production and enrichment of additional bioactive metabolites of medicinal importance including isoflavones, saponins, phytosterols, and phenols. For example, the phenolic contents of the herbal preparation can be increased as a consequence of fermentation and a positive correlation between polyphenols and the anti-oxidant activities of herbs has been well demonstrated. This is in agreement with evidence showing fermentation-mediated enhancement of the pharmacological properties and therapeutic efficacies of herbal formulations against a number of diseases including obesity and inflammation. The subject of fermentation of herbal preparations has been maturing and gaining considerable attention of scientific and technical communities worldwide. In the current review we have addressed these issues in detail with emphasis on understanding the contribution of fermentation-derived bioactive substances to therapies against a number of diseases.

Contents

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1. Introduction

Fermentation is a microorganism-driven process which yields high value product from raw or low grade substrates. More specifically, fermentation breaks down or converts the undesirable substrates into compatible components under the action of microbial enzymes, thereby improving the substrate properties via the production and enrichment of bioactive compounds (Parvez, Malik, Ah Kang, & Kim, 2006). In addition, fermentation improves the nutrient values of foods and also breaks them down into more easily catabolisable forms.

Herbal drugs have been implicated as traditional medicines for thousands of years (Xutian, Zhang, & Louise, 2009). Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products, that contain as active ingredients parts of plants, or other plant materials, or combinations (General guidelines for methodologies on research and evaluation of traditional medicine, World Health Organization, Geneva, 2000). Herbs include crude plant material such as leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered. While herbal materials include, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs (General guidelines for methodologies on research and evaluation of traditional medicine, World Health Organization, Geneva, 2000). Therefore, herbal medicines encompass a vast area of plant products some of which are also edible. As there is no universal 'gold standard' for herbal medicines and because of the legal requirements for categorization of herbal medicines vary from countries to countries, many of these products often cross the borderline of regulated categories of goods such as foods and cosmetics.

Based on an approximate estimation, it has been opined by World Health Organization (WHO) that more than three-quarters of population of the developing nations use herbal medicines for their primary health care (Luqman, Rizvi, Beer, Khare, & Atukeren, 2014). A variety of components of herbs have been isolated and their biological activities are assessed (Lee, Lee, & Jin, 2012). Substantial evidence supports the usefulness of herbs in treating various human diseases, disorders and illness (Luqman et al., 2014). However, many of the herbal medicines require biotransformation by microbiota in the large intestine in order to become biologically active (Lee et al., 2012), indicating the need of fermentation in the therapeutic application of herbal drugs. Because of the emerging knowledge on beneficial health effects of probiotics and their fermented food products (Parvez et al., 2006), the use of fermented herbal medicines has been escalated over time. The fundamentals of microbial fermentation and transformation of traditional herbal medicine can be outlined into the following features (Wu, Wang, Zhang, & Xu, 2013) (1) microorganism in the growing phase can generate a variety of biologically active macro-molecules like protease, amylase, cellulase, esterase and amidase which are the members of synthase and decomposing enzyme families. These enzymes are the key players in the chemical reaction(s) involved in medicinal fermentation process as they decompose the herbal medicines and convert them into new entities; (2) many microbes can use active herbal ingredients as substrates to produce new compounds, and simultaneously the secondary metabolites of these microorganisms and herbal medicines can also interact each other to form new compounds; (3) some substances in the herbal drugs can alter the metabolic pathways of microorganisms, and thereby can produce new ingredients; (4) herbal drugs may be concentrated because microorganism can consume non-medicinal components, such as proteins, sugars and other substances during their growth phase.

In addition to the above, herbal fermentation is also known to be associated with several biochemical changes, resulting in altered ratio of nutritive and anti-nutritive components of the plants, which ultimately affect product properties like bioactivity and digestibility (Heiniö et al., 2003; Katina et al., 2007). Fermentation-mediated bio-activation of the herbal medicines results in improved therapeutic potencies and efficacies and decreased toxicities where the microbial population plays a pivotal role (Lin, Wang, Lee, & Su, 2008; Miyake et al., 2005; Nakano et al., 2006; Wu et al., 2013). Fermentation improves the pharmacological properties of herbal medicines mainly through the modification of naturally occurring molecules such as isoflavones, saponins, phytosterols, and phenols that exert beneficial health-promoting and disease-preventing effects, in keeping with the 'theory of the oriental medicine' (Choi & Kang, 2003). For the past few years, with the rapid progress in microbial fermentation technologies and in-depth research on the modernization of herbal medicines, the microbial fermentation and transformation of herbal drugs have gained considerable interest and appeared as new approaches to produce novel active compounds with potent medicinal values (Wu et al., 2013).

2. Fermentation-mediated improvement of bioactivity of herbal medicines

The fermentation of medicinal herbs, a decomposition process, is performed by using microorganisms such as bacteria and fungi. Fermentation is considered to be one of the most useful techniques of biocatalytical process which is a feasible method for the production of new, active, and less toxic bioactive products that would be otherwise troublesome to generate from either biological systems or chemical synthesis (Rasor & Voss, 2001). In the course of the metabolic breakdown of the substrates, microbes release several compounds apart from the usual products of fermentation (generally carbon dioxide and ethanol), especially during the lag phase of microbial growth. These additional compounds, also called secondary metabolites, range from several antibiotics to peptides, pigments, enzymes, and growth factors (Balakrishnan & Pandey, 1996; Machado, Oishi, Pandey, & Soccol, 2004; Robinson, Singh, & Nigam, 2001). These compounds have diverse biological activities such as anti-infective, anti-inflammation and anti-cancer, and are hence referred to as bioactive compounds. Table 1 depicts fermentation-mediated enhancement in the bioactive substances or compounds in some of the vital herbal medicines.

Fermentation process induces the structural breakdown of plant cell walls, leading to the liberation or synthesis of various anti-oxidant compounds (Hur, Lee, Kim, Choi, & Kim, 2014). For example, it has been shown that during the course of *Lactobacillus*-mediated fermentation, organic acids are amassed, proteins are hydrolyzed and anti-oxidant ferulic acid from plant cell wall materials is solubilized (Cheigh, Park, & Lee, 1994; Eriksson & Na, 1995). Consistent with these, it has been found that *Aspergillus oryzae*-mediated fermentation facilitates the formation of strong anti-oxidants that destroy free radicals (Minamiyama et al., 2007), supporting the notion that the fermented plant products are abundant in anti-oxidants (Hur et al., 2014). The fermentation is also known to exert beneficial effects on the absorption and bioavailability of herbal extracts by facilitating the production or conversion of active components into their metabolites or by generating low molecular weight substances such as aglycone from glycoside (Bae et al., 2004; Joo et al., 2009). In addition, several lines of evidence indicate that the fermentation