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# Chinese Herbal Medicines

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## Editorial

### Deepening insights into food and medicine continuum within the context of pharmacophylogeny

The concept of food and medicine continuum (FMC) is traced back to *Shennong's Classic of Materia Medica* (Shénnóng Běncào Jīng in Chinese) of the 1st century (Heinrich et al., 2022), which recorded 120 herbal medicines of the 'top grade' with nourishing properties; they can be consumed for extended periods of time without obvious side effects, indicating their functional food and medicinal benefits (Xiao, 2023). In recent decades, the health-promoting actions of numerous edible herbal medicines and phytometabolites therein have been scrutinized. For instance, many FMC plants, such as *Panax ginseng* C. A. Mey., *Camellia sinensis* (Linn.) O. Ktze., *Ganoderma lucidum* (Leyss. ex Fr.) Karst., *Lycium barbarum* L., etc., display effects of enhancing immunity (Pan et al., 2023; Yao et al., 2023). The benefits of dietary interventions and phytometabolites on improving cognitive functions in elderly population have been supported by accumulating evidence (Heinrich et al., 2022). Therefore, food and medicine dual-use products are important in the prevention and intervention of chronic diseases and senile illnesses. Due to the different historical and cultural backgrounds of the East and the West, as well as the huge differences in geographical environment, physique and resources, the eating/medication habits are also distinct between East and West, which have established unique standards and knowledge systems for FMC products, and have different ways, purposes and methods of using the same FMC species or phylogenetically related species (Xiao, 2023). The list for FMC substances of China includes 109 entities, which are from 151 species (Yao et al., 2023). However, in Europe only 37 of these species are very important in healthy food use, and 86 of them are not used for healthy food. Strengthening the research and knowledge dissemination of Oriental FMC within the phylogenetic framework, consistent with the oriental systematic thinking, will help to improve the regulatory standards for FMC items, reduce barriers to communication, and make FMC more effective for the benefit of all mankind.

Nature presents a wonderful scene of food and medicine dual use, which brings endless fun to human rational thinking, no matter macro or micro. This issue has several outstanding papers that demonstrate the unremitting pursuit of human beings in exploring FMC substances. For instance, the phytochemistry analysis displayed that the main components of *Benincasae Exocarpium* (the dried outer pericarp of *Benincasa hispida* (Thunb.) Cogn.) are flavonoids, alkaloids, tannins, trace elements and vitamins (Zhang et al., 2023), and 43 compounds have been reported at present. The tea polyphenols, e.g., flavan-3-ols, flavonol glycosides, theanine, caffeine, are the most important compounds for both bioactivities

and flavors, which are abundant in both black tea/oolong tea and dark tea (Pan et al., 2023)/Kombucha (Selvaraj & Gurumurthy, 2023). Additionally, the enriched metabolites via microbial fermentation form the mellow, sweet, and smooth taste of dark tea. Such metabolites include but not limited to prenylated cyclic dipeptides, B-vitamins, anthraquinones, flavan-3-ol B-ring fission analogues, fatty acids, triterpenoids, guanidine derivatives, cholesterol, lipopeptides, acarbose, asperphenamate, prenylated benzaldehydes, among others. Similarly, Kombucha is made from black tea via microbial fermentation (Selvaraj & Gurumurthy, 2023), which contains abundant organic acids, amino acids, vitamins, probiotics, sugars, polyphenols, and antioxidants. It could be intriguing to compare the fermentation metabolome of dark tea and Kombucha, and reveal the underlying microbial mechanisms via multiple omics techniques. It is interesting to treat *Benincasae Exocarpium* with fermentation microbiota to see whether its metabolome, flavor and health-promoting bioactivities could be further improved, so as to enrich the value-added products derived from FMC materials. Based on experimental analyses of phytochemistry and bioactivity of FMC materials, the medicinal/edible compounds and properties of related plants can be predicted by virtue of phylogenetic methods (Hao, Lyu, Wang, & Xiao, 2022a; Hao, Zhang, He, & Xiao, 2022c), which nevertheless has not been utilized to explore the regularity of most ethnomedicinal and edible species. It is promising to investigate the distribution of the specific compound type and/or efficacy of ethnomedicinal/edible plants on the species-level Tree of Life, so as to more effectively tap health food resources.

Tea has a deep history as the first Chinese herbal medicine used by the Chinese. Modern pharmacological studies and clinical practice showed that *Benincasae Exocarpium* has diuretic, hypolipidemic, hypoglycemic, antioxidant, antibacterial, and antiviral effects (Zhang et al., 2023), which has long been used as a material of tea. Kombucha, originated in northeast China and is popular abroad, possesses anti-inflammatory, anti-carcinogenic, antimicrobial, antioxidant, anti-proliferative activities (Selvaraj & Gurumurthy, 2023). The bioactivities of dark tea are also diverse, including antioxidation, anti-bacteria, anti-inflammation, anti-obesity, anti-diabetes, anti-diarrhea, anti-cancer, gastrointestinal regulation, cardiovascular protection, immune-regulation, hepatoprotection, neuroprotection, and photoprotection (Pan et al., 2023). In contrast to these advances, the pharmacokinetic/pharmacodynamic (PKPD) studies of these FMC materials are far less enough, and there is gap in the awareness of absorption, distribution, meta-

bolism, excretion and toxicity (ADMET) attributes of many FMC products. Despite numerous reports about beneficial effects of FMC materials, it is difficult to determine the chemical basis of different therapeutic and health effects, for which studies of ADMET properties must be taken into account, including the elucidation of gut microbiota mediated transformation (Hao et al., 2022b). The phylogenetically closer species are more likely to have similar phytometabolome, but FMC chemicals with the same/similar structural type might have analogous or reverse ADMET properties, which warrant case-by-case elaborations in the context of pharmacophylogeny. Facing the competition of western medicine, the identity of herbal medicine is always in crisis, and it must constantly redefine itself in the landscape of evolving new theories and technologies. It is important to provide consumers with the recommended, minimum, and maximum daily doses of FMC products (Pan et al., 2023). The optimal duration of intake to achieve a significant preventive and ameliorating effects of diseases should also be carefully studied.

At the beginning of the birth of FMC, art, science and technology were interrelated. The overlapping and intertextuality of art, science and technology on FMC jointly defined FMC. In the contemporary era when western medicine has overwhelming advantages, most of the health benefits and non-toxicity of FMC materials have not been scientifically validated in human body. Clinical trials are yet to be done to manifest the claimed health benefits. Of note, most FMC studies focus on either *in vitro* screening in cell culture or network pharmacology speculations based on data from *in silico* and/or simple cell culture models (Hao et al., 2022b). In the future, the clinical trials of FMC products have to be conducted as open label with placebo, covering enough number of subjects, and should focus on symptomatic benefits. The clinical studies are expected to generate PKPD insights as well. With any luck, findings from such research could strengthen consumers' confidence and recognition of FMC, as legitimate prevention and treatment option. Actually, the recent COVID-19 outbreak in major cities could help generate real-world data on the use of TCM (including FMC), which provide appreciated insights on their utilities.

Last but not least, as the food and/or drink, the proper sensory evaluation should be performed to provide a vibrant view of the flavor profile, the consumer's desire, and acceptance (Selvaraj & Gurumurthy, 2023). Many FMC substances are traditionally used as food and listed in the Chinese Pharmacopoeia, which have both the efficacy of TCM and the safety of traditional food, therefore they play a vital role in health care. However, people often overemphasize the safety of FMC products in the clinical application, but ignore their application principles, function characteristics, application forms and dietary taboos, thus resulting in ineffectiveness

and even harm to health. Pharmaceutical researchers must master the concept and connotation of FMC, and also learn more about food science and engineering. Under the guidance of TCM theory, researchers and clinicians need to use the dialectical thinking, apply FMC materials based on syndrome differentiation, reasonably mix them, adjust measures to people and local conditions, and grasp the functions and characteristics of FMC products, which can not only demonstrate the effectiveness of TCM, but also further ensure the safety of FMC application as food, so as to benefit the healthy development of standardization, modernization and internationalization of FMC products.

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