International Journal of Food Science + Technology

International Journal of Food Science and Technology 2017, **52**, 13–21

Review

Metabonomics: a developing platform for better understanding Chinese herbal teas as a complementary therapy

Rong You,[1]* Yanqing Guan[1] & Lin Li[2]

1 College of Life Sciences, South China Normal University, 55 Zhongshan Avenue West, Guangzhou 510631, China
2 College of Light Industry and Food Sciences, South China University of Technology, 381 Wushan Road, Guangzhou 510640, China

(Received 4 April 2016; Accepted in revised form 18 June 2016)

Summary Chinese herbal teas (CHTs) have gained increasing attention throughout the world as a complementary therapy. Due to the multicomponent composition in herbal teas, the molecular mechanisms of their causality in health effects are still elusive and becoming the main obstacles for their application. There is a pressing need for a more systematic study about their molecular mechanisms to substantiate the health effects of CHTs. With the particular feature of measuring the real metabolic phenotype resulted from molecular interplay between host and environmental factors, metabonomics is especially suited to inspect metabolic responses to CHT intake and provide insights into health effects. Application of metabonomics to uncover the effects of CHTs on human health is foreseen as providing deeper insights of the complicated molecular mechanisms of CHTs by explaining relatively subtle and different effects of herbal tea intervention, classifying the metabolic responses to herbal tea, depicting synergistic effects of CHTs and evaluating the safety of CHTs intake.

Keywords Chinese herbal teas, complementary therapy, metabonomics, molecular mechanisms.

Introduction

Chinese herbal teas (CHTs), also known as *Liangcha* or cooling tea in China, are commonly consumed decoctions or infusions made from a variety of medicinal or edible herbals. The main herbs used in CHTs preparation and the related health effects were shown in Table 1 together. The preparation of CHTs by the combined use of different herbs was originated in southern China two hundred years ago, which could be used as an effective therapy to drive away the uncomfortable feelings and prevent the diseases like influenza and encephalitis (Yang *et al.*, 2014). Now herbal teas have been refined over long history and used to alleviate the symptoms of *Shanghuo* as a complementary and functional therapy. *Shanghuo*, a traditional Chinese medicine (TCM) conception, represents a disorder of physiological homoeostasis under different stresses (Rongrong & Hiroshi, 2008) with the syndromes of gingival swelling and sore throat (Ge *et al.*, 2011; Liu *et al.*, 2014) etc. According to TCM viewpoints, CHTs intervention could maintain body homoeostasis through avoidance of overheating and inadequate energy level. This putative explanation was just based on the following assumptions: (i) herbs with different natures and flavours are complementary to each other and (ii) the combined use of different herbs is beneficial to health condition and could adjust the whole physiological state to obtain the metabolic homoeostasis (Koo, 1989). This means that the effects of CHTs intervention might entails a 'network' approach, in which multiple compounds interact *in vivo* with multiple targets to achieve optimal effects like preventing free radical damage, detoxifying and improving immunity and so on. However, how CHTs exert such modulating effects on human health remains unknown.

Perceived as healthy beverages, Chinese herbal teas have been identified as one of the nonmaterial cultural heritages in China. At present, there are many brands of Chinese herbal teas in the market such as Wang Laoji, Bai Yunshan and Huang Zhenlong. Meanwhile, the growing market is expanded from China to all around the world including USA, Canada, Australia, Japan and France (Liu *et al.*, 2013). CHTs are obviously gaining more and more appreciation for health promotion and disease prevention. While CHTs were inherited from traditional preparation, the interest about herbal teas is now being harnessed to develop a

*Correspondent: Fax: +86 20 85215535;
e-mail: yourong@scnu.edu.cn

doi:10.1111/ijfs.13206

Table 1 The herbs involved in Cantonese herbal tea

Main herbs	Family	Related health effects validated by *in vitro* or *in vivo* tests
Ilex asprella	*Oroxylum indicum*	Antiviral effects *in vitro* Zhou *et al.* (2012b), attenuation of acute respiratory distress syndrome *in vivo* Dai *et al.* (2014)
Lophatherum gracile	*Gramineae*	Antiviral effects *in vitro* Wang *et al.* (2011)
Vitex negundo	*Rutaceae*	Antioxidative effects *in vitro* Tiwari & Tripathi (2007)
Microcosm paniculata	*Tiliaceae*	Antibacterial
Oroxylum indicum	*Bignoniaceae*	Antimicrobial and anti-inflammatory effects *in vitro* Ali *et al.* (1998); antioxidative effects *in vitro* Yan *et al.* (2011)
Rosa laevigata michx	*Rosaceae*	Antioxidative activity *in vitro* and hypolipidemic activity *in vivo* Liu *et al.* (2010), renal protective effects *in vivo* Zhou *et al.* (2012c)
Lygodium japonicum	*Lygodiaceae*	Antioxidative and antimicrobial effects *in vitro* Li *et al.* (2006)
Desmadium styracifolium merr	*Leguminosae*	Antilithic and antioxidative effects *in vivo* Mi *et al.* (2011), Xiang *et al.* (2015)
Polygonum chinense	*Polygonaceae*	Anti-ulcerogenic effects *in vivo* Olatunji *et al.* (2015), gastroprotective effects *in vivo* Ismail *et al.* (2012)
Helicters angustifolia	*Fimiana*	Antidiabetic activity *in vivo* Bhat *et al.* (2012)

new generation of herbal tea according to the standardisation and specialisation production. However, there is increasing concern about the effects on health and possible side effects as a lack of supportive scientific evidences pertaining to its health effects (Vanja *et al.*, 2014). It is still difficult to decipher the complex links between CHTs intake and human health, and it is even harder to make nutritional recommendations for CHTs intake. Obviously, great efforts in explaining CHTs' effects on human health should be made to accelerate the development of herbal tea industry. In this review, the authors presented developments and challenges in evaluating the health effects associated with CHTs intake and elaborated how metabonomics would become an exploratory and unique approach to understanding CHTs effects on human health.

Developments in substantiating the health claims associated with CHT intervention

When it comes to exploring and proving the efficacy and safety of CHTs, a variety of investigations have been carried out with the attempt to find the clues on the identity of CHTs relevant for health beneficial effects. Phytochemical analysis, as a key step to assess the characteristics and effectiveness of different herbal teas, was extensively performed (Carbonara *et al.*, 2012; Zhao *et al.*, 2013). Consequently, different platforms with the merits of high-throughput analysis, high sensitivity and excellent specificity were developed to simultaneously analyse the main active components in different herbal formulas. For instance, some phenolic acid-containing compounds were separated and confirmed by HPLC in Guangdong herbal tea extracts to understand the antistress effects (He *et al.*, 2011). RPLC-MS analytical method was developed for the identification and determination of the major constituents in Deng's herbal tea, most of which were chlorogenic acids, flavonoids and liquiritins (Deng *et al.*, 2011). Capillary zone electrophoresis was also used to fully separate and quantitatively determine more than thirty major constituents in CHTs, which included different types of flavonoids and phenolic acids like linarin, liquiritin and rutin so on (Chi *et al.*, 2009). Hence, those identified polyphenols and flavonoids were putatively thought to contribute their health effects significantly. The pharmacological investigations of the identified polyphenols and flavonoids were further carried out to explain the anti-inflammatory, antioxidant and antiviral effects of CHTs (Atoui *et al.*, 2005). In all, the present investigations developed the intermediate connections between CHTs intake and health effects and provided an avenue for deeper understanding their molecular mechanisms.

Challenges in uncovering the molecular mechanisms of action of CHTs intake

As mentioned above, the presence of polyphenols and flavonoids in CHTs was usually attributed to exert their effects on human health. However, the identified polyphenols and flavonoids could not represent the total composition in herbal teas; and what is more, the assembly of their efficacies obtained could not represent the concerted effects of CHTs intervention. To uncover the molecular mechanisms of effects of CHTs intake, the two levels of complexity including the diversity of phytochemicals in CHTs and the complexity of their biological effects are needed to take into account. From the authors' viewpoints, there are obvious challenges in mining the molecular mechanisms of action of CHTs intake through traditional assessments and some new and powerful tools should be applied to understand the cause-and-effect relationship.

To begin with, holistic medicine holds that herbal remedies work better when the whole complex of plant phytochemicals is kept together than when these chemicals are purified and administered singly (McKee, 1988). The preparation of herbal tea was made according to the complementary rules of different flavours and natures, and thus, the effects of CHTs on organisms could not be obtained by current evaluating system. It also means that the combinational effects are greater than the sum of the individual effects, which is defined as synergistic function of multicomponent therapeutics (Sun *et al.*, 2014). Accordingly, the explanation of CHTs' molecular mechanisms could not be obtained by assembling the pharmacological effects of individual phytochemicals in herbal teas. Evaluation of CHT's health effects should be more based on the synergistic effects as a whole.

Secondly, herbal teas processing will have an impact on the variation of composition because many types of chemical reactions may occur during processing like hydrolysis, oxidation, isomerisation and decomposition and so on (Zhao *et al.*, 2013). Generally, the most commonly used method is heating including steaming, roasting and decocting for different purpose, which was operated at high temperature (above 100 °C) to cause variation and transformation of certain phytochemicals. Du-shen-tang, a decoction of the root of Panax ginseng, is a commonly used TCM prescription to restore normal pulse, benefit the spleen and anchor the minds (Jin *et al.*, 2012). There are forty-five major ginsenosides identified in Du-shen-tang and twenty-one of which were newly generated during decocting of ginseng (Li *et al.*, 2010). Thus, the constituent variations during herbal tea preparation will produce the new constituent profiling different from the ingredients in raw materials. Therefore, the identified ingredients may be different from the active substances in herbal tea and the effects of these ingredients may not be very reliable.

Finally, emerging evidence suggests that diet and herbal medicines interact strongly with the gut microbiome. This means that the phytochemical constituents of herbal teas will undergo complicated biotransformation in the intestine like hydrolysis, reduction, aromatic heterocyclic, cracking, decarboxylation, halogen, dealkylation and so on (Bohn, 2014). Polyphenols are generally considered as the active components of many herbs associated with beneficial health effects, which go through complicated biotransformations like deglycosylation, dehydroxylation and demethylation mediated by gut microbiota (van Duynhoven *et al.*, 2011). As a consequence, some small number of phenolic acids would be absorbed from the colon for liver metabolism. Hence, the *in vitro* effects of identified ingredients from raw materials could not represent the real effects of herbal teas on human health.

Taking together, the diversity of the constituents in herbal tea and the complexity of their biological effects caused a lack of explaining the molecular mechanisms of effects of herbal tea on human health. The analytical and pharmacological methods arising from the philosophy of 'reductionism' could not conquer these predicaments in CHTs studies. To address these challenges, unravelling the complex metabolic interaction between herbal tea and human biological system might be extremely important for the resolution of this seemingly insurmountable dilemma. The advent of metabonomics, characterised by high-throughput biochemical analyses coupled with bioinformatics, has made us able to resolve this intractable issue.

Metabonomics: a systematic and widely approach to unravel the real readout of the organism after stimulus

Defined as 'the quantitative measurement of the dynamic multi-parametric metabolic response of living systems to pathophysiological stimuli or genetic modification' (Nicholson *et al.*, 1999), metabonomics has become one of the most hopeful systematic methods and been successfully applied in many areas such as pharmacology (Lindon *et al.*, 2007; Kaddurah-Daouk & Weinshilboum, 2015), diagnosing or prognosing clinical diseases (Brindle *et al.*, 2002; Bjerrum *et al.*, 2010; Kinross *et al.*, 2011; Zhu *et al.*, 2014; Öhman & Forsgren, 2015; Chu *et al.*, 2016) and toxicology (Xie *et al.*, 2009; Van *et al.*, 2015). The concept of metabonomics is to generate complex data from various applications of NMR and MS spectroscopy and detect changes in the distribution and concentration of metabolites with multivariate analysis, which can produce pathway information, measure subtle perturbations of pathways resulting from genetic and environmental factors (Trygg *et al.*, 2007) and provide metabolic phenotypes with respect to environmental, diet and genetic modulations etc. (Fig. 1). Hence, metabonomics has been successfully performed for the assessment of relationships between dietary components and health maintenance (Solanky *et al.*, 2005; Cuparencu *et al.*, 2016), dietary habits and blood pressure (Holmes *et al.*, 2008), caloric restriction and ageing (Wang *et al.*, 2007) etc. In recent years, metabolomics has also been applied to characterise organisms' global metabolic responses to phytochemical intervention through depicting the endogenous metabolome changes (Jang *et al.*, 2016). Such metabolic changes provided globally true association between phytochemicals intervention and effects on human health. Meanwhile, metabolomics is increasingly used to investigate the phytochemical metabolome and identify new markers of phytochemical exposure, which is of crucial importance for mapping the metabolic fate of phytochemicals (Dorsten *et al.*, 2010), knowing how phytochemicals are metabolised and classifying the metabolic pattern of individual responses to phytochemicals intake (Bondia-Pons *et al.*, 2013; Velzen *et al.*, 2014). Moreover, these

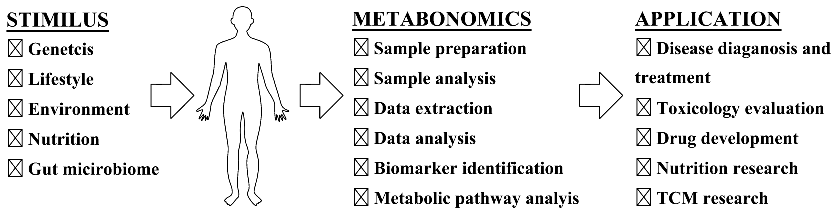

Figure 1 The outline of metabonomics research and applications.

exposure metabolome might have an effect beyond their antioxidant properties by interacting with some signalling pathways implicated in important processes (Shankar *et al*., 2013; Ferguson, 2014) and also significantly affect endogenous metabolism, leading to quantitative changes in endogenous metabolites. And thus, endogenous metabolome and exogenous phytochemical metabolome form a special signature characteristic of the intake of given phytochemicals.

Considering relatively subtle and multifactorial effects of CHTs intervention, the observed modulations are hard to evaluate through traditional assessments. One of greatest scientific challenges in CHTs investigations is to decipher the inherently inextricable metabolic interactions between herbal tea and human metabolism and to understand its modulating role in human health. Through the rigorous characterisation of interactions between the diet, human metabolism and the microbiota, metabonomics is providing new ventures for characterisation of CHT effects on human health. So the process after herbal tea intake can be considered as a plant metabolome interacting with human biological system. Metabonomics will simultaneously produce the information about human endogenous metabolome changes and phytochemicals exposure level, which will reflect the global and systematic effects of CHTs on human biological system through specific modulating pathway.

In all, the state-of-the-art metabonomics has become the first optional method to achieve further and deeper mechanistic studies of action of CHT intervention as a sensitive strategy. Here, we will present special advantages of metabonomics application in CHT investigations.

Special advantages of metabonomics applied in Chinese herbal tea research

(1) Metabonomics is coming to grip with relatively subtle and different effects of herbal tea intervention and identify exposure biomarkers for different herbal tea intake.

The highly complicated composition in herbal tea and subtle effects of herbal teas impeded the investigations about the molecular mechanisms. Metabonomics is powerful in evaluating the metabolic fate of a given dietary intervention and disclosing the complex interactions between multicomponent dietary ingredients and the human metabolic regulatory system. This systematic method has substantial compatibility with TCM theory and great potentials to be able to overcome the confounding reasons and permit the study of the system-wide effects of CHTs and provide an in-depth understanding of its mechanisms of action and health benefits (Lan & Jia, 2010). In our previous study, metabolomics strategy was performed to investigate the global biological characterisation associated with Cantonese herbal tea intervention in normal rats (You *et al*., 2012). The results showed that the overall metabolic responses to Cantonese herbal tea intervention were reflected in the variations of energy metabolism, lipid metabolism and amino acid metabolism etc., leading to a direct elucidation of the mechanisms of action of Cantonese herbal tea. Our studies clearly demonstrate that herbal tea-induced metabolic modulations were a result of complex interactions between the complicated herbal tea system and the whole-organism system. We also found that Cantonese herbal tea intake counteracted oxidative stress in restrain-stressed rats and restored the disturbed metabolic pathways to normal level, which suggested that Cantonese herbal tea had the ability of maintaining body homoeostasis (You *et al*., 2014). Hence, metabonomics is ideally positioned to allow mechanistic studies of action of Chinese herbal tea intervention as a sensitive strategy and explain the molecular mechanism after herbal tea administration.

Originated from TCM viewpoints, the effects of Chinese herbal teas on human health can be classified into four categories such as relieving the syndrome of cold, moisturising dry-heat, detoxifying and clearing away internal heat and dampness. Although some of them have common effects, different formulas of herbal teas should have different effects on human health. However, there are no specific guidance associated with these different herbal teas as a complementary therapy. So how can these subtle effects among different CHTs be differentiated? This is vital for the consumers to choose herbal tea. In general, foods with different composition will produce different impacts on the human metabolome. After CHTs ingestion, phytochemicals in CHTs may appear in the serum, faeces, or urine, either unchanged or chemically modified by microbial or mammal metabolism. Metabonomics can be used to characterise CHTs exposure and identify particular phytochemical metabolites associated with different herbal tea intake. Such metabolites can be considered as the novel and robust biomarkers of CHTs exposure and will be valuable for choosing CHTs. In fact, metabonomics strategies have been applied to investigate the different responses after different dietary exposure (Van Dorsten *et al*., 2006; Jov *et al*., 2011), which shows that metabonomics has great potentials to differentiate the subtle metabolic changes between dietary intervention.

Based on above-mentioned discussions, metabonomics strategy could be reasonably used to delineate the metabolic responses after CHTs intervention and obtain some useful biomarkers associated with different herbal tea intervention.

(2) Metabolomics is trying to classify the metabolic patterns after CHTs intake

It is known that the physiological and metabolic responses to a drug or dietary treatment can strongly vary among humans (Becker *et al*., 2011). Genotypic diversity, lifestyle and gut microbial variations are important and known factors contributing to these intrinsic variations (Nicholson *et al*., 2012). Hitherto, the investigation to explain the complex and subtle interactions between herbal tea intervention and human health is also confronted with the additional source of complexity attributable to inherent individual variations. The ideal method should phenotype individual's responses to a drug or dietary intervention in a holistic and systematic manner, which integrates all the factors including genetics, gut microbiota and physiology status. As metabolic profiles encapsulate information on genetics, environmental factors, gut microbiota activity, lifestyle and food habits, metabonomics provides an exploratory but unique opportunity to depict the molecular mechanisms involved in individual responses to drug or dietary modulations.

An conceptually new 'pharmaco-metabonomic' approach to personalise drug treatment was developed to by Clayton *et al*. (2006), which presented a means to characterise the individual responses to drug treatment. This may ultimately provide new insights into the role of personalised healthcare programs. It also means that metabonomics can characterise individual response to dietary modulations. Recently, the strategy based on the metabolic profiling and nutrikinetics multilevel paired PLSDA was developed and became a very powerful method to classify individual metabolic phenotypes after black tea intake (van Velzen *et al*., 2009; van Duynhoven *et al*., 2012). The research about different metabolic response to daily chocolate consumption was also carried and came to the conclusion that the dietary preference for dark chocolate in healthy subjects led to different metabolic response to daily chocolate consumption (Martin *et al*., 2012). It suggested that the human metabolome are shaped coherently by genotype, lifestyles and gut microbiota etc., and metabonomics can differentiate biological variations and discern individual responses to dietary interventions.

Collectively, these studies suggested that the combined application of metabonomics and nutrikinetics could offer novel perspectives for phenotyping individuals to dietary intervention and can be used to classify the different metabolic pattern and allowing a deeper understanding the different dietary intake. Likewise, this integral metabonomic technology can be used to classify different metabolites pattern after exposure to the complex plant extracts. So individual metabolic phenotype can be achieved through the combined use of metabonomics and nutrikinetics as illustrated in Fig. 2. This method can be considered as a very promising way to predict how different individuals will respond to CHTs treatment.

(3) Metabonomics is trying to delineate the synergistic effects of CHTs intake on human health

Many scientists are kept going with the discovery and identification of active ingredients in CHTs' raw materials (Horžić *et al*., 2009). Such investigation aimed at the determination of the single active components in plants, based on the assumption that one dominant or a few ingredients determined the therapeutical effects. However, these methods could not measure the global and maximum efficacy and systematically explore the modes of action of combined mixtures of CHTs. Actually the multicomponent in herbal medicine would unexpectedly produce synergistic effects, that is to say, the combined effects will be greater than the sum of individual effects, making multicomponent therapeutics as a systematic approach. It has been realised that the synergistic effects must be taken into account when evaluating the biological effects of all different plant extracts. Moreover, a growing body of convincing evidences have demonstrated that the combinational and synergistic effects should play a great role in regulating the network and provide the basis of multicomponent therapeutics (Kan *et al*., 2008; Wang *et al*., 2008; Zhang *et al*., 2011). The reason of the synergistic effects in multicomponent herbal formula might be related to the fact that the combinations of different ingredients can effectively reduce side effects and target a molecular network to adjust the imbalance in a systematic manner. Likewise, there should be the same conditions in the multicomponent herbal teas used to alleviate different symptoms caused by '*shanghuo*'.

Metabonomics is a newly developed method to provide variations of the whole metabolic networks for characterising pathological states. As an effective and

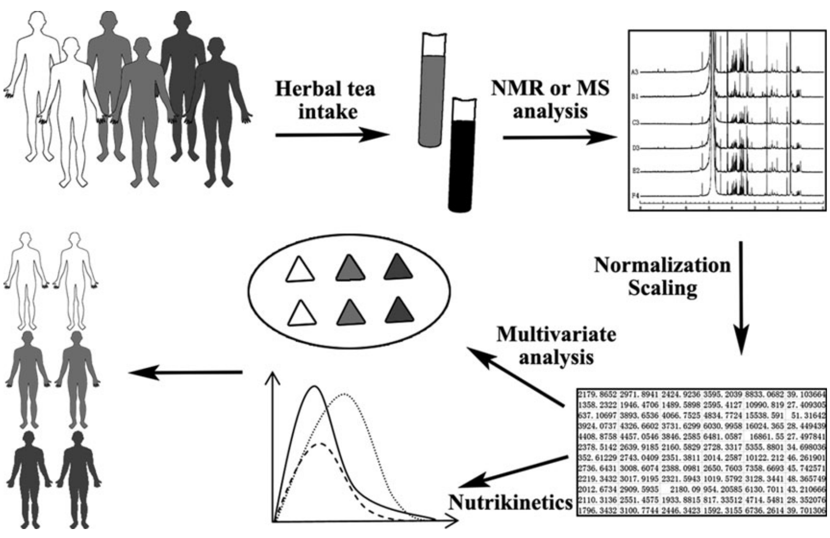

Figure 2 The metabolic phenotype classified by metabonomics and nutrikinetics.

powerful method, metabonomic strategies have been shown that it can conquer the impediments to explore the synergistic therapeutic efficacies of some herbs (Liang *et al.*, 2010; Zhou *et al.*, 2012a). However, few investigations were carried out on the synergy effect of herbal tea. Maybe metabonomics can be used to study the synergistic effects among these different ingredients and obtain the deeper understanding of the health effects and side effects about herbal tea intervention.

(4) Metabonomics is trying to evaluate the safety of CHTs intake.

Although CHTs are intended to provide health benefits for consumers, their increasing use as complementary and functional therapy has triggered significant concerns amongst scientific communities (Ivković *et al.*, 2014). Given the multicomponent nature, subtle effects and the low budgets available safety assessment have been seldom carried out for CHTs research. Till now there has been few scientific data to establish the safety of functional herbal. The safety of herbal tea usually relies on the quality control for adulterants and contaminants and mastery of complex processing methods (Deng & Yang, 2013) etc. These measures are, however, inadequate or insufficient for evaluating complex mixtures of incompletely known component and mild effects, where adverse events may take several months or even years to manifest (Williamson *et al.*, 2015). So there is a pressing need for development risk assessment strategies to establish the safety margin between CHTs exposure and potential hazard.

The major issue of safety assessment is the highly complexity of the components contained in CHTs. So it is difficult to make use of classical risk assessment methods like toxicological and pharmacokinetic studies for herbal tea safety evaluation. Metabonomics is a powerful tool which can provide the comprehensive metabolites profiling in biofluids, reflect the changes of metabolites concentrations and fluxes involved in different metabolic pathways and thereby give an indication of an organism's physiological or pathophysiological status (Nicholson *et al.*, 2002). And thus, metabonomics has high-priority in the pharmaceutical industry for safety and toxicity assessments. Wand has been developed as an effective strategy to reflect specific toxicity and track progression of toxicity over a time period (Lindon *et al.*, 2006, 2011). We can reason out that metabonomics becomes a powerful method for not only assessing the molecular mechanism of action of CHTs but also gaining insights into the extent to which CHTs intervention will influences the whole organism. As such, metabonomics with bioinformatics techniques will make it possible to investigate the safety and toxicity of CHTs intervention.

Taking together, all these special and powerful advantages of metabonomics strategy made metabonomics capable to study the causality in exerting health effects. Although herbal tea is complicated in its composition containing different polyphenols, alkaloids, flavonoids etc., metabonomcis has the great potentials to obtain the deeper understanding of the health effects and side effects about herbal tea intervention.

Future research

The metabolic relationship between herbal tea ingestion and human health is still poorly characterised, which hampered our understanding the molecular mechanisms of action of CHTs intake. Undoubtedly, metabolomics approach will be the most powerful platform for the mechanistic research of CHTs as it does not require any prior knowledge of the exact composition of the dietary intake and can provide a better understanding of the underlying mechanism, which will encapsulate the information about genetic background, environmental factors and lifestyles. Therefore, metabonomics should be considered as a very promising way to shed light on the mystery of CHTs. The state-of-the-art metabonomics harbour the possibility to identify the biomarkers for CHTs intervention and explain the molecular mechanisms of action of CHTs. It is also expected that metabonomics will generate new visions of health effects and side effects caused by herbal tea intervention.

Acknowledgment

We are grateful to thank for the financial supports by Science and Technology Planning Project of Guangdong Province (No. 2015A020212033).

Authorship

This review is drafted and written by Rong You and revised by Yanqing Guan and Lin Li.

Conflict of interests

There are no real or perceived conflict of interests from intellectual, personal or financial circumstances of the research.

References

Ali, R.M., Houghton, P.J., Raman, A. *et al.* (1998). Antimicrobial and antiinflammatory activities of extracts and constituents of *Oroxylum indicum* (L.) Vent. *Phytomedicine*, **5**, 375–381.

Atoui, A.K., Mansouri, A., Boskou, G. *et al.* (2005). Tea and herbal infusions: their antioxidant activity and phenolic profile. *Food Chemistry*, **89**, 27–36.

Becker, N., Kunath, J., Loh, G. *et al.* (2011). Human intestinal microbiota. *Gut Microbes*, **2**, 25–33.

Bhat, B.A., Muthukumar, T., Sethupathy, S. *et al.* (2012). Evaluation of anti-diabetic activity of *Helicters isora* fruit extract in alloxan induced diabetic rats. *Journal of Pharmacy Research*, **5**, 2830–2833.

Bjerrum, J., Nielsen, O., Hao, F. *et al.* (2010). Metabonomics in ulcerative colitis: diagnostics, biomarker identification, and insight into the pathophysiology. *Journal of Proteome Research*, **9**, 954–962.

Bohn, T. (2014). Dietary factors affecting polyphenol bioavailability. *Nutrition Reviews*, **72**, 429–452.

Bondia-Pons, I., Cañellas, N., Abete, I. *et al.* (2013). Nutri-metabolomics: subtle serum metabolic differences in healthy subjects by NMR-based metabolomics after a short-term nutritional intervention with two tomato sauces. *OMICS: A Journal of Integrative Biology*, **17**, 611–618.

Brindle, J., Antti, H., Holmes, E. *et al.* (2002). Rapid and noninvasive diagnosis of the presence and severity of coronary heart disease using ^{1}H-NMR-based metabonomics. *Nature Medicine*, **8**, 1439–1445.

Carbonara, T., Pascale, R., Argentieri, M.P. *et al.* (2012). Phytochemical analysis of a herbal tea from *Artemisia annua* L. *Journal of Pharmaceutical and Biomedical Analysis*, **62**, 79–86.

Chi, L., Li, Z., Dong, S. *et al.* (2009). Simultaneous determination of flavonoids and phenolic acids in Chinese herbal tea by beta-cyclodextrin based capillary zone electrophoresis. *Microchimica Acta*, **167**, 179–185.

Chu, H., Zhang, A., Han, Y. *et al.* (2016). Metabolomics approach to explore the effects of Kai-Xin-San on Alzheimer's disease using UPLC/ESI-Q-TOF mass spectrometry. *Journal of Chromatography B*, **1015–1016**, 50–61.

Clayton, T.A., Lindon, J.C., Cloarec, O. *et al.* (2006). Pharmacometabonomic phenotyping and personalized drug treatment. *Nature*, **440**, 1073–1077.

Cuparencu, C.S., Andersen, M.B.S., Gürdeniz, G. *et al.* (2016). Identification of urinary biomarkers after consumption of sea buckthorn and strawberry, by untargeted LC–MS metabolomics: a meal study in adult men. *Metabolomics*, **12**, 1–20.

Dai, W.P., Li, G., Li, X. *et al.* (2014). The roots of Ilex asprella extract lessens acute respiratory distress syndrome in mice induced by influenza virus. *Journal of Ethnopharmacology*, **155**, 1575–1582.

Deng, J. & Yang, Y. (2013). Chemical fingerprint analysis for quality assessment and control of Bansha herbal tea using paper spray mass spectrometry. *Analytica Chimica Acta*, **785**, 82–90.

Deng, J., Fan, C. & Yang, Y. (2011). Identification and determination of the major constituents in Deng's herbal tea granules by rapid resolution liquid chromatography coupled with mass spectrometry. *Journal of Pharmaceutical and Biomedical Analysis*, **56**, 928–936.

Dorsten, F.A.V., Grün, C.H., Velzen, E.J.J.V. *et al.* (2010). The metabolic fate of red wine and grape juice polyphenols in humans assessed by metabolomics. *Molecular Nutrition & Food Research*, **54**, 897–908.

van Duynhoven, J., Vaughan, E.E. & Jacobs, D.M. (2011). Metabolic fate of polyphenols in the human superorganism. *Proceedings of the National Academy of Sciences of the USA*, **108**(Suppl. 1), 4531–4538.

van Duynhoven, J., van Velzen, E., Westerhuis, J. *et al.* (2012). Nutrikinetics: concept, technologies, applications, perspectives. *Trends in Food Science & Technology*, **26**, 4–13.

Ferguson, L.R. (2014). Nutritional modulation of gene expression: might this be of benefit to individuals with Crohn's disease? *Frontiers in Immunology*, **6**, 467.

Ge, N., Gong, J., Ni, S. *et al.* (2011). "Shanghuo" "Inflammatory" and the relationship between free radicals. *Journal of Liaoning University of Traditional Chinese Medicine*, **2**, 87–89.

He, R.R., Tsoi, B., Li, Y.F. *et al.* (2011). The anti-stress effects of Guangdong herbal tea on immunocompromise in mice loaded with restraint stress. *Journal of Health Science*, **57**, 255–263.

Holmes, E., Loo, R., Stamler, J. *et al.* (2008). Human metabolic phenotype diversity and its association with diet and blood pressure. *Nature*, **453**, 396–400.

Horžić, D., Komes, D., Belščak, A. *et al.* (2009). The composition of polyphenols and methylxanthines in teas and herbal infusions. *Food Chemistry*, **115**, 441–448.

Ismail, I.F., Golbabapour, S., Hassandarvish, P. *et al.* (2012). Gastroprotective activity of polygonum Chinense aqueous leaf extract on ethanol-induced hemorrhagic mucosal lesions in rats. *Evidence-based Complementary and Alternative Medicine*, **2012**, 277–293.

Ivković, V., Karanović, S., Prlić, M.F. *et al.* (2014). Is herbal tea consumption a factor in endemic nephropathy? *European Journal of Epidemiology*, **29**, 221–224.

Jang, H.-J., Kim, J.W., Ryu, S.H. *et al.* (2016). Metabolic profiling of antioxidant supplement with phytochemicals using plasma 1H NMR-based metabolomics in humans. *Journal of Functional Foods*, **24**, 112–121.

Jin, X., Zhu, L.-Y., Shen, H. *et al.* (2012). Influence of sulphur-fumigation on the quality of white ginseng: a quantitative evaluation of major ginsenosides by high performance liquid chromatography. *Food Chemistry*, **135**, 1141–1147.

Jov, M., Serrano, J.C.E., Ortega, N. *et al.* (2011). Multicompartmental LC-Q-ToF-based metabonomics as an exploratory tool to identify novel pathways affected by polyphenol rich diets in mice. *Journal of Proteome Research*, **10**, 3501–3512.

Kaddurah-Daouk, R. & Weinshilboum, R. (2015). Metabolomic signatures for drug response phenotypes: pharmacometabolomics enables precision medicine. *Clinical Pharmacology and Therapeutics*, **98**, 71–75.

Kan, W.L.T., Cho, C.H., Rudd, J.A. *et al.* (2008). Study of the antiproliferative effects and synergy of phthalides from *Angelica sinensis* on colon cancer cells. *Journal of Ethnopharmacology*, **120**, 36–43.

Kinross, J., Alkhamesi, N., Barton, R. *et al.* (2011). Global metabolic phenotyping in an experimental laparotomy model of surgical trauma. *Journal of Proteome Research*, **10**, 277–287.

Koo, L.C. (1989). Ethnonutrition in Hong Kong: traditional dietary methods of treating and preventing disease. *The Hong Kong Practitioner*, **11**, 221–231.

Lan, K. & Jia, W. (2010). An integrated metabolomics and pharmacokinetics strategy for multi-component drugs evaluation. *Current Drug Metabolism*, **11**, 105–114.

Li, X.L., Zhou, A.G. & Yong, H. (2006). Anti-oxidation and antimicroorganism activities of purification polysaccharide from Lygodium japonicum in vitro. *Carbohydrate Polymers*, **66**, 34–42.

Li, S.L., Lai, S.F., Song, J.Z. *et al.* (2010). Decocting-induced chemical transformations and global quality of Du–Shen–Tang, the decoction of ginseng evaluated by UPLC–Q-TOF-MS/MS based chemical profiling approach. *Journal of Pharmaceutical and Biomedical Analysis*, **53**, 946–957.

Liang, X., Chen, X., Liang, Q. *et al.* (2010). Metabonomic study of Chinese medicine Shuanglong formula as an effective treatment for myocardial infarction in rats. *Journal of Proteome Research*, **10**, 790–799.

Lindon, J.C., Holmes, E. & Nicholson, J.K. (2006). Metabonomics techniques and applications to pharmaceutical research & development. *Pharmaceutical Research*, **23**, 1075–1088.

Lindon, J., Holmes, E. & Nicholson, J. (2007). Metabonomics in pharmaceutical R & D. *FEBS Journal*, **274**, 1140–1151.

Lindon, J.C., Nicholson, J.K. & Holmes, E. (2011). *The Handbook of Metabonomics and Metabolomics*. 279. Amsterdam: Elsevier Science.

Liu, Y.T., Lu, B.N., Xu, L.N. *et al.* (2010). The antioxidant activity and hypolipidemic activity of the total flavonoids from the fruit of Rosa laevigata Michx. *Natural Science*, **2**, 175–183.

Liu, Y., Ahmed, S. & Long, C. (2013). Ethnobotanical survey of cooling herbal drinks from southern China. *Journal of Ethnobiology and Ethnomedicine*, **9**, 82.

Liu, S., Huang, Z., Wu, Q. *et al.* (2014). Quantization and diagnosis of Shanghuo (Heatiness) in Chinese medicine using a diagnostic scoring scheme and salivary biochemical parameters. *Chinese Medicine*, **9**, 2.

Martin, F.-P.J., Montoliu, I., Nagy, K. *et al.* (2012). Specific dietary preferences are linked to differing gut microbial metabolic activity in response to dark chocolate intake. *Journal of Proteome Research*, **11**, 6252–6263.

McKee, J. (1988). Holistic health and the critique of Western medicine. *Social Science and Medicine*, **26**, 775–784.

Mi, J., Duan, J., Zhang, J. *et al.* (2011). Evaluation of antiurolithic effect and the possible mechanisms of Desmodium styracifolium and Pyrrosiae petiolosa in rats. *Urological Research*, **40**, 151–161.

Nicholson, J., Lindon, J. & Holmes, E. (1999). 'Metabonomics': understanding the metabolic responses of living systems to pathophysiological stimuli via multivariate statistical analysis of biological NMR spectroscopic data. *Xenobiotica*, **29**, 1181–1189.

Nicholson, J., Connelly, J., Lindon, J. *et al.* (2002). Metabonomics: a platform for studying drug toxicity and gene function. *Nature Reviews Drug Discovery*, **1**, 153–162.

Nicholson, J.K., Holmes, E., Kinross, J. *et al.* (2012). Host-gut microbiota metabolic interactions. *Science*, **336**, 1262–1267.

Öhman, A. & Forsgren, L. (2015). NMR metabonomics of cerebrospinal fluid distinguishes between Parkinson's disease and controls. *Neuroscience Letters*, **594**, 36–39.

Olatunji, O.J., Chen, H. & Zhou, Y. (2015). Anti-ulcerogenic properties of Lycium chinense mill extracts against ethanol-induced acute gastric lesion in animal models and its active constituents. *Molecules*, **20**, 47–72.

Rongrong, H. & Hiroshi, K. (2008). Shanghuo syndrome in traditional chinese medicine. *World Science and Technology*, **10**, 37–41.

Shankar, S., Kumar, D. & Srivastava, R.K. (2013). Epigenetic modifications by dietary phytochemicals: implications for personalized nutrition. *Pharmacology & Therapeutics*, **138**, 1–17.

Solanky, K., Bailey, N., Beckwith-Hall, B. *et al.* (2005). Biofluid ^{1}H NMR-based metabonomic techniques in nutrition research-metabolic effects of dietary isoflavones in humans. *Journal of Nutritional Biochemistry*, **16**, 236–244.

Sun, Y., Liu, Q. & Cao, Z. (2014). *Data Analytics for Traditional Chinese Medicine Research*. Pp. 81–96. New York: Springer.

Tiwari, O.P. & Tripathi, Y.B. (2007). Antioxidant properties of different fractions of Vitex negundo Linn. *Food Chemistry*, **100**, 1170–1176.

Trygg, J., Holmes, E. & Lundstedt, T. (2007). Chemometrics in metabonomics. *Journal of Proteome Research*, **6**, 469–479.

Van Dorsten, F.A., Daykin, C.A., Mulder, T.P. *et al.* (2006). Metabonomics approach to determine metabolic differences between green tea and black tea consumption. *Journal of Agricultural and Food Chemistry*, **54**, 6929–6938.

Van, d.E.N., Cuykx, M., Rodrigues, R.M. *et al.* (2015). Metabolomics analysis of the toxicity pathways of triphenyl phosphate in HepaRG cells and comparison to oxidative stress mechanisms caused by acetaminophen. *Toxicology in Vitro*, **29**, 2045–2054.

Vanja, I., Sandra, K., Margareta, F.T.P. *et al.* (2014). Is herbal tea consumption a factor in endemic nephropathy? *European Journal of Epidemiology*, **29**, 221–224.

Velzen, E.J.J.V., Westerhuis, J.A., Grün, C.H. *et al.* (2014). Population-based nutrikinetic modeling of polyphenol exposure. *Metabolomics*, **10**, 1059–1073.

van Velzen, E.J.J., Westerhuis, J.A., van Duynhoven, J.P.M. *et al.* (2009). Phenotyping tea consumers by nutrikinetic analysis of polyphenolic end-metabolites. *Journal of Proteome Research*, **8**, 3317–3330.

Wang, Y., Lawler, D., Larson, B. *et al.* (2007). Metabonomic investigations of aging and caloric restriction in a life-long dog study. *Journal of Proteome Research*, **6**, 1846–1854.

Wang, X.N., Han, X., Xu, L.N. *et al.* (2008). Enhancement of apoptosis of human hepatocellular carcinoma SMMC-7721 cells through synergy of berberine and evodiamine. *Phytomedicine*, **15**, 1062–1068.

Wang, Y., Chen, M., Zhang, J. *et al.* (2011). Flavone C-glycosides from the leaves of Lophatherum gracile and their in vitro antiviral activity. *Planta Medica*, **78**, 46–51.

Williamson, E.M., Chan, K., Xu, Q. *et al.* (2015). Evaluating the safety of herbal medicines: integrated toxicological approaches. *Science*, **347**(Suppl.), S47–S49.

Xiang, S., Zhou, J., Jing, L. *et al.* (2015). Antilithic effects of extracts from different polarity fractions of Desmodium styracifolium on experimentally induced urolithiasis in rats. *Urolithiasis*, **43**, 433–439.

Xie, G., Zheng, X., Qi, X. *et al.* (2009). Metabonomic evaluation of melamine-induced acute renal toxicity in rats. *Journal of Proteome Research*, **9**, 125–133.

Yan, R.Y., Cao, Y.Y., Chen, C.Y. *et al.* (2011). Antioxidant flavonoids from the seed of *Oroxylum indicum*. *Fitoterapia*, **82**, 841–848.

Yang, Z.F., Bai, L.P., Huang, W.b. *et al*. (2014). Comparison of in vitro antiviral activity of tea polyphenols against influenza A and B viruses and structure–activity relationship analysis. *Fitoterapia*, **93**, 47–53.

You, R., Xu, Z., Hu, S. *et al*. (2012). Characterization of temporary metabolic changes following Cantonese Herbal Tea intervention. *Phytotherapy Research*, **26**, 1097–1102.

You, R., Pang, Q. & Li, L. (2014). A metabolic phenotyping approach to characterize the effects of cantonese herbal tea on restraint stressed rats. *Biological &/and Pharmaceutical Bulletin*, **37**, 1466–1474.

Zhang, A., Sun, H., Yuan, Y. *et al*. (2011). An in vivo analysis of the therapeutic and synergistic properties of Chinese medicinal formula Yin-Chen-Hao-Tang based on its active constituents. *Fitoterapia*, **82**, 1160–1168.

Zhao, J., Deng, J., Chen, Y. *et al*. (2013). Advanced phytochemical analysis of herbal tea in China. *Journal of Chromatography A*, **1313**, 2–23.

Zhou, M., Wang, S., Zhao, A. *et al*. (2012a). Transcriptomic and metabonomic profiling reveal synergistic effects of quercetin and resveratrol supplementation in high fat diet fed mice. *Journal of Proteome Research*, **11**, 4961–4971.

Zhou, M., Xu, M., Ma, X.X. *et al*. (2012b). Antiviral triterpenoid saponins from the roots of Ilex asprella. *Planta Medica*, **78**, 1702–1705.

Zhou, Y., Liao, Q., Luo, Y. *et al*. (2012c). Renal protective effect of Rosa laevigata Michx. by the inhibition of oxidative stress in streptozotocin-induced diabetic rats. *Molecular Medicine Reports*, **5**, 1548–1554(1547).

Zhu, J., Djukovic, D., Deng, L. *et al*. (2014). Colorectal cancer detection using targeted serum metabolic profiling. *Journal of Proteome Research*, **13**, 4120–4130.

