Proteomics Approach Reveals Importance of Herbal Plants in Curing Diseases

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Abstract
Herbalism (also herbal medicine) is a science that includes curing diseases by using plant derived compounds. Herbal medicine has important role in curing many diseases and it has very long history worldwide. Compared to single constituent dosage medicines, herbal medicines exhibit combined therapeutic action and can increase the risk of cytotoxicity caused by chemotherapeutic treatments. Proteomic techniques have been applied to study the physiology of medicinal plants and their effects on animals to understand the mechanism involved in pharmacological nature of plants. This review focus on the present status of proteomic research on medicinal plants and covers metabolic pathways involved in synthesis of bioactive compounds; pharmacological studies; and proteomics application to indigenous plants in disease curing. Pool of proteomic knowledge in a biological and medicinal context can boost the effective use of medicinal plants.
Keywords: Drug, Herbal, Medicinal plants, Protein expression.

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INTRODUCTION

The role of medicinal plants is of backbone in herbal medicines and biomedical innovation throughout the world. Discovery of many conventionally used therapeutic drugs based upon the traditional knowledge of medicinal plants and further improved by scientific validation. One of the remarkable discovery of the world of herbal medicines is "Paclitaxel" an anticancerous drug derived from *Taxus brevifolia* (Weaver *et al.,* 2014). A large number of plant-based potential drug components are still unidentified aside from the large-scale screening of herbal products underway (Atanasov *et al.,* 2015). These active compounds are difficult to identify due to the presence of several other secondary metabolites and the complexity of the metabolic pathway involved in their biosynthesis (Vogt *et al.,* 2016). Environmental effects on genetic and physiological responses of plant sum up to the synthesis of secondary metabolites. In single plant species, considerable differences are found in the biosynthesis of active compounds like saponins and flavonoids (Hashiguchi *et al.,* 2017). Transcription factors play important roles to drive different pathways by regulating gene expression (Fatima *et al.,* 2018). Chemical reactions cause extensive modifications in the biosynthetic pathways of medicinal plants and multiple drug compound subfamilies are produced by glycosylation steps from branch points of metabolic pathways (Plaza *et al.,* 2014). This suggests that for identification of active compounds, understanding of the systemic regulation of metabolic pathways in medicinal plants is very important.

Aside from the therapeutics and drug potentials of medicinal plants, several compounds, and their biosynthetic pathways are undiscovered that can be potential sources of the medical field. Many medicinal plants are not known for their pharmacological applications. For the proper utilization of metabolic products and genetic resources of plants, physiological investigations on secondary metabolites production and pharmacological effects of active compounds on animals are useful directions for future studies of medicinal plants. Comprehensive physiological information of medicinal plants and animals using these plants can be collected by proteomics studies. Discovery of key enzymes has explicated the complex metabolic pathways of biologically active compounds. Proteomic studies depict the changes in physiological activities and metabolic pathways caused by external factors. Various biological processes were shown responses of animals treated with herbal drugs. In medicinal herb's research, these studies are side by side linked to each other. Research on medicinal plants can be boosted by increasing collaborative multidisciplinary research that includes both fields.

Importance of medicinal plants in drug discovery

Isolation from natural sources, plants, synthetic chemistry etc. are various techniques have been utilized to discover the drug compounds further combinatorial natural products have proven themselves as new chemical entities (NCE) and natural products and their derivatives from 1981 to 2002 shared 28% of NCEs. Study of natural compounds during this time provided another 20% NCEs (Newman *et al.,* 2003). So, the research on natural medicinal compounds during 1981-2002 reported 48% of NCEs. For the synthesis of very challenging new synthetic compounds with multiple stereo centers and diverse structures, natural compounds provide a starting point (Koehn and Carter, 2005). Complex ring systems, aromatic rings, chiral centers, number and ratio of heteroatoms and molecule saturation degree etc. are very common to natural drugs and relative to efforts for drug discovery (Piggott and Karuso, 2004). Furthermore, with the increasing interest in combinatorial chemistry and with the realization that these compound libraries are not always diverse, many synthetic and medicinal chemists are trying to explore the creation of natural-product-like libraries and natural products that combine the compound generating a potential of combinatorial chemistry with structural features of natural products (Tan *et al.,* 2004). Medicinal plants-based compounds can be used directly as new drugs or after some synthetic and medicinal optimizations. Already known compounds having new biological activity are good drug leads while discovering new drugs from medicinal plants when new chemical structures are not found. Previous studies documented that plant extracts possess antibacterial and antifungal activities (Kalim *et al.,* 2016; Hussain *et al.,* 2016; Shahzad *et al.,* 2017; Al-Deen and Al-Jobory, 2018).

Sequencing of the human genome revealed the importance of thousands of new molecular targets in diseases (Kramer and Cohen, 2004). The possible selective activity of medicinal plants-based drug compounds may be assessed for these target points with the help of high-throughput screening assays. From traditional medicinal plants known drug compounds have shown to act on newly identified molecular targets, indirubin is an example that selectively acts on cyclin-dependent kinase and inhibits it (Eisenbrand *et al.*, 2004) and kamebakaurin inhibits the NF-nB (Lee *et al.*, 2004). Such responses for many other compounds have been noticed that's increasing the interest in the classes of these plant-derived compounds. Examples include the; cucurbitacin-I is a diverse set of known compounds, obtained from the National Cancer Institute act with activated STAT3 selectively inhibits the JAK/STAT3 pathway in tumors (Blaskovich *et al.*, 2003), cancer cells during cell cycle are actively killed by h-lapachone during direct checkpoint activation (Li *et al.*, 2003) and with activated p38, betulinic acid is selectively cytotoxic to melanocytes tumors (Cichewicz and Kouzi, 2004).

Proteomics and medicine

Mostly commercial plant species were the focus of above mentioned syntenic studies. For mango that produces mangier in (a unique xanthonoid) catalog of

protein was provided (Andreu *et al.,* 2005). To extract the small amount of protein existing in mango pulp and banana, protein purification method with more advancement was provided by Liao et al. (2016). Proteomics profiles of traditionally used medicinal plants *Pseudostellaria heterophylla*, *Moringa oleifera* and *Nigella sativa* have already been published (Alanazi *et al.,* 2006). Protein extraction protocol has optimized for cosmetically important seagrass species *Posidonia australis* and *Zostera muelleri* that contain hundreds of bioactive compounds (Jiang *et al.,* 2017). A Proteomics study has been carried out for a tropical plant *Zingiber zerumbet* to evaluate the intervention of epigenetics in carotenoid biosynthesis (Mahadevan, 2016). Aside from the elaboration of the physiological systematic changes in medicinal plant science, proteomics also contributes to identifying the enzymes involved in drug compounds production. In Asian countries, commonly used herb *Centella asiatica* has become famous containing saponins as active compounds (Gray *et al.,* 2017). Saponin is modified by multiple glycosylations; triterpenoid carboxylic acid (UDP-glucose 28-O-glucosyltransferase) was successfully isolated glycosyltransferase for this modification (de Costa *et al.,* 2017). The appropriate use of proteomics techniques can help to discover metabolic pathways and unique enzymes. Lack of genetic information and the complexity of secondary metabolites which is mostly species-specific are major constraints for the study of medicinal plants. Although genome sequences for some species are available (Hodzic *et al.,* 2017), but transcriptomics the basis for studying secondary metabolites is gaining its importance (Han *et al.,* 2016). Now transcriptomics data based on RNA-seq is available for many plants including *Dendrobium officinale* (Shen *et al.,* 2017), *Ephedra sinica* (Okada *et al.,* 2016), *Polygonum minus* (Loke *et al.,* 2016), and *Dioscorea nipponica* (Sun *et al.,* 2017). To understand the unique properties of some diverse plants like pitcher plant, some tropical and medicinal plants were studied by RNA-seq based transcriptomic analysis (Zulkipli *et al.*, 2015). Using RNA sequencing high throughput sequences are obtained and stored in public data repositories which can be reanalyzed (Sansone and Bromberg, 2012).

Proteomics and herbal medicines

The proteomic approach is now used in the treatment of many diseases (Figure 1). Proteomics is merging as a new area to transform the biology and medicine, mostly protein functions are regulated not only by post-translational modifications of mRNA but also protein localization, so protein expression is poorly correlated with mRNA expression (Zaynab *et al.,* 2017a; Zaynab *et al.,* 2018). Thus, proteomic studies are concerned to elaborate protein expression and functions, to fully understand the working of biological systems proteomics will be combined with other information including gene profiles and mRNA metabolites.

Comprehensive knowledge of traditional Chinese medicines can be exactly mapped by integrated proteomic approaches. Proteomic approaches have been used to understand the mode of action and pharmacological effects of CTM, in future can be used to identify new bioactive compounds and target molecules.
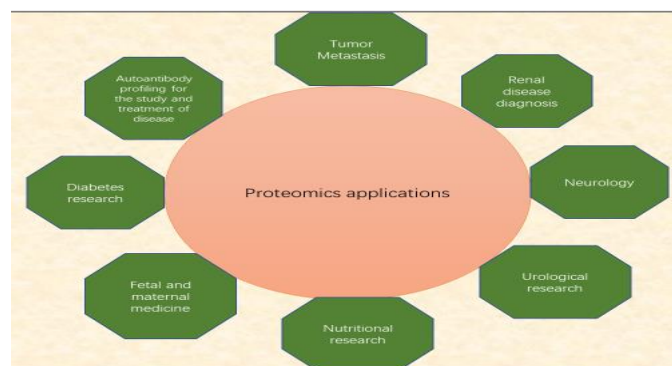

Fig. 1. Proteomics Application in disease curing

Now mass spectrometry-based two techniques are being commonly used for quantitative protein profiling including proteins labeled with isotope tags separated by mass spectrometry and multidimensional liquid chromatography and two-dimensional electrophoresis followed by mas-spectrometry based staining, identification and selection (Figure 2) (Zaynab *et al.,* 2017b; Weston and Hood, 2004). Molecular imaging can supplement both of the approaches. In zebra fish flavonoids metabolism from *Herba epimedii* have been studies by the combined use of *in vivo* imaging and proteomic approaches (Li *et al.*, 2011). Identification of new species is one of the implications of proteomics in CHM as in the case of Panax (*P. ginseng vs. P. quinquefolium*) (Lum *et al.*, 2002). For traditional Chinese medicines, proteomics will be a very important tool for toxicity studies, quality control, standardization of TCM preparations, which are the key points CHM use in the western world. Proteomic studies just like transcriptomics and genomics have successfully described the mode of action of different TCM preparations, as the effect of Si WU Tang decoction on the general health (Guo *et al.*, 2014) effects of *Salvia miltiorrhiza* on atherosclerotic lesions (Hung *et al.*, 2010), *Ganoderma* properties in nerve injury (Zhang *et al.*, 2014) and the effects of several other preparations in cancer have been investigated at the proteomic level (Hung *et al.*, 2010). Further in myocardial ischemia repair effect of shuanglong TCM formula on differentiation and use of pluripotential cells has also been investigated by proteomics data (Fan *et al.*, 2010). Proteomics is becoming an important tool for exploring the diverse effects of complex herbal preparations, development of active functions, the discovery of bioactive compounds, molecular diagnosis and a safe prescription for TCM treatments in spite of the difficult

interpretation of proteomics due to the inherent complexity of the components in TCM decoctions.
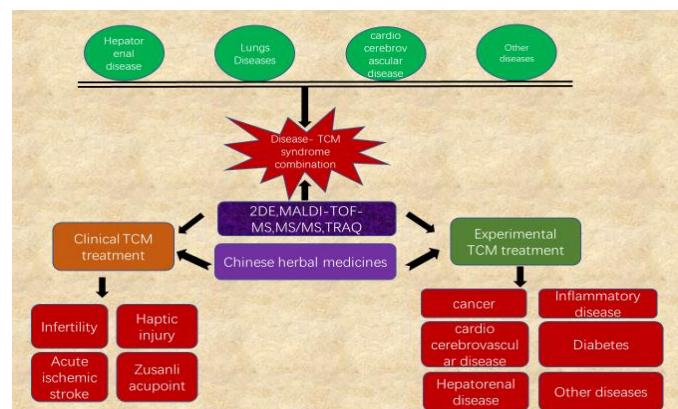

Fig. 2. Quantitative proteomics in disease curing

CONCLUSION

Many natural compounds and their metabolic pathways that can be important for the medical field are still undiscovered. Several pharmaceutical properties of medicinal herbs are remaining to elucidate. Physiological studies of plant's secondary metabolites and pharmacological effects of plant-based drugs on animals are important research areas for utilizing the genetic potential of medicinal plants. Proteomics provides global information on medicinal plants and their effects on animals. Discovery of key metabolic enzymes has elaborated the complex biosynthetic pathways of drug compounds. Proteomic approaches have enabled us to understand the physiological changes associated with external factors. Plant drugs treated animal's responses elaborated various biological pathways. Proteomic studies of secondary metabolites and the drug-treated animal's responses are of key importance, and collaborative multidisciplinary research can improve the science of medicinal plants.

CONFLICT OF INTEREST

The authors declare that no competing interests exist.

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