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Commentary on: Proteomic Analysis of Apoptosis Induction by Lariciresinol in Human HepG2 Cells

Zhan Jun Ma[1], Xue Xi Wang[2,*]

1 The Second Clinical School, Lanzhou University, Lanzhou, Gansu, China;
2 School of Basic Medical Sciences, Lanzhou University, Lanzhou, Gansu, China.

*Corresponding author. Tel: +86 931 891 1119; E-mail: wangxuexi@lzu.edu.cn

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Commentary

Traditional Chinese Medicine (TCM) has been used for thousands of years in China and is thus a valuable aspect of traditional Chinese culture. However, TCM involves complex chemical systems, making the study of its mechanisms of action very difficult [1]. Part of this complexity is due to the diversity of sources of TCM, including drugs derived from plants, animals, and minerals. These various sources of raw materials have led to a wide range in the chemical constituents of TCM, and the resultant diversity of compounds has in turn led to multiple effects on organs due to the multiple roles and targets of these compounds. Additionally, the clinical application of TCM is primarily based on compound formulae, and the issue of compatibility among multi-compound herbal medicines makes TCM even more complex and difficult to study. Studies of compound formulae are needed not only to elucidate the biological activity of the chemical constituents in each unilateral formula, but also to study the compatibility and synergy among the various unilateral formulae. Therefore, there is an urgent need to apply new technologies to the study of the mechanisms of complex TCM systems.

Systems biology, which was first proposed by Leroy Hood in 1999, refers to all components in a biological system and involves studies of the relationships among these components under specific conditions. Systems biology may provide breakthroughs in the study of TCM because its concepts are consistent with the holistic philosophy of Chinese medicine [2]. Systems biology, which involves genomics, epigenomics, proteomics and metabolomics, seeks to describe the complex interactions among the components of biological systems and thus predict the behavior of the biological system. Proteomics technology, a major component of systems biology, has gained considerable attention in the area of medical diagnosis, drug development, and mechanism research [3]. Since proteins are the major executers of biological activities, proteomics analysis provides a direct reflection of gene expression. Proteomics approaches include two-dimensional electrophoresis (2-DE), mass spectrometry and bioinformatics. 2-DE provides a useful tool for rapid profiling of cellular factors differentially responding to a drug treatment [4]. With respect to holistic and systemic theory, proteomics can converge with TCM and overcome the biases present in TCM research [5]. First, proteomics may be used to characterize the differential expression profiles between healthy individuals and patients with different TCM syndromes. Second, proteomics can identify altered proteins as potential drug targets, and the global analysis of protein alterations can help clarify a drug's mechanism of action. Through analysis of these protein changes in tissue and cultured cells before and after TCM treatment, proteomics is a powerful tool with which to study the mechanisms of action of TCM remedies [6].

Within this context, we report in this issue of *Chemico-Biological Interactions* that lariciresinol (LA) inhibited cell proliferation and induced apoptosis in HepG2 cells *in vitro* according to the results of a proteomic analysis [7]. We also found that the molecular pathway of cell apoptosis in LA-treated HepG2 cells might be related to the ubiquitin-proteasome pathway (UPP). First, we extracted LA from *Patrinia scabra* Bunge and determined the chemical structure of LA. Next, we observed the cytotoxicity in LA-treated HepG2 cells. LA significantly inhibited cell growth and promoted apoptosis and induced S-phase arrest in HepG2 cells, which may have contributed to growth inhibition. Furthermore, using a proteomics approach, eight differentially expressed proteins were identified in HepG2 cells in response to LA treatment and protein–protein interactions were analyzed using STRING software, version 9.1, a Web-based bioinformatics search tool for interacting proteins. Our findings suggest that the UPP plays an important role in the mechanism of LA-induced apoptosis of HepG2 cells. Finally, the results of Western blotting for key proteins were consistent with those of 2-DE and STRING analyses. Overall, these findings provide strong evidence that LA is a multitarget compound with anticancer effects potentially involving the UPP. However, as with any scientific discovery, these findings raise numerous questions that must be resolved through further research. First, the differentially expressed

proteins were mainly distributed on the acidic side, and only eight differentially expressed proteins were successfully identified. Two-dimensional gel electrophoresis should be performed to characterize the differential expression profiles with pH 4–7 immobilized pH gradient strips in response to LA treatment. Additionally, bioinformatics analysis tools should be applied to identify the key target proteins and related signal networks of target proteins that interact in TCM. Future research should also explore the effects of specific molecular mechanisms on LA-induced cytotoxicity because the UPP can influence and regulate apoptosis through multiple pathways, including the mitochondria-dependent apoptotic pathway and the death receptor-mediated pathway. Besides, STITCH tool is a database of known and predicted interactions between chemicals and proteins; it also can be used for this study to predict the LA and proteins. Finally, as we all known, chemical constituents of TCM may possess activities altering post-translational modifications (PTMs) which mainly contain protein phosphorylation, acylation, glycosylation, ubiquitination, acetylation, oxidation, methylation, etc. PTMs affect protein structure and act as molecular switches, which regulate the interaction of proteins with DNA, cofactors, lipids, and other proteins [8]. Modification-specific proteomic approaches combined with advanced MS/MS methods and bioinformatics data analysis have revealed a surprisingly large extent of PTMs in proteins, including multi-site, cooperative modifications in individual proteins [9]. Therefor future study might explore the effects of PTMs on HepG2 cells with LA-induced cytotoxicity through modification-specific proteomic approaches.

TCM researchers have widely recognized the rationality and feasibility of applying systems biology to the study of complex systems. High-throughput proteomics technologies assist the researchers to identify candidate proteins, which play key roles in TCM treatment response and toxicity. Proteomics is a current hot topic in the field of systems biology, and proteomics as applied to the study of complex TCM systems will undoubtedly facilitate new medical developments. However, proteomics technology has limitations and disadvantages [5]. Relatively fewer proteins have been identified by proteomics technology than by genomics and transcriptomics. The results of proteomics studies are frequently unstable and variable, meaning that the reproducibility of proteomics data is poor. To obtain ideal results, it is necessary to combine other technologies (bioinformatics, Western blot, siRNA, iTRAQ and others) to achieve many of the objectives of TCM research [10]. Although the application of proteomics to TCM research is challenging, the importance of proteomics is noticeable because of the fact that in a majority of cases neither the genomic sequence itself nor the transcriptional profile can be associated directly with protein expression and gene function although the completion of the Human Genome Project that provides the basis for a better understanding of cellular and molecular mechanisms of human physiology and diseases. In short, as a major component of systems biology, proteomics provides a very good opportunity for the modernization and internationalization of TCM.

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