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Mini Review

Bufalin's Pro Government Adenocarcinoma Molecular and Metabolic Mechanisms: Fresh and Detailed Data from Network Pharmacology, Metabolomics, and Molecular Biology Investigations

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Abstract

By a thorough approach incorporating network pharmacology, metabolomics, and molecular biology verification, this study seeks to assess the therapeutic efficacy and mechanism of bufalin on lung cancer. The Swiss Target Prediction database and Pharm Mapper were used to identify the possible targets of bufalin. Target filtering of the Gene Card database and data mining of the GEO database were used to find LUAD-related targets. The core targets were screened using a PPI network, and the clinical importance of each target was evaluated using a number of open databases. To find potential enrichment of genes with particular biological topics, GO and KEGG pathway studies were carried out. To ascertain the correlation and binding pattern between bufalin and core targets, molecular docking and molecular dynamics modelling were used. The network-predicted methods via which bufalin affects LUAD In-vitro and in-vivo models were used to experimentally validate the pharmacological analyses. Finally, non-targeted metabolomics was used to examine how bufalin intervention affected the metabolite profile and metabolic pathway in LUAD nude mice. 51 junction targets were found among the 1082 LUAD-associated and bufalin targets that were extracted. Using network topology analysis, 10 main targets, including Akt1, STAT3, EGFR, CASP3, and SRC, were identified. Molecular docking and MD simulations revealed that these targets exhibited a strong affinity for bufalin. Cell proliferation and death were tightly correlated with the hub module of the PPI network. Bufalin was found to be effective in treating LUAD by suppressing proliferation and inducing apoptosis via the PI3K/Akt, FoxO1, and MAPK/ERK pathways, as revealed by GO and KEGG enrichment analyses. This was supported by a number of subsequent studies. Of in-vitro research and the tumour tissues' HE, TUNEL, and Ki-67 staining. Bufalin largely controlled ABC transporter regulation and altered AA metabolism, which helped treat LUAD, according to further metabolomics study. The current study, which successfully filtered out associated key target genes, differential endogenous metabolites, and signalling pathways, not only provided a unique insight into the potential mechanisms of bufalin against LUAD from a molecular and metabolic perspective, but also suggested a novel, promising therapeutic approach for LUAD.

Keywords: Bufalin, Network pharmacology, Metabolomics, Lung adenocarcinoma, Molecular biology

INTRODUCTION

The most frequently diagnosed histological subtype of non-small cell lung cancer with the greatest fatality rate worldwide is lung adenocarcinoma (Melchart D., et al 1998). Despite significant advancements in recent decades in multimodal treatment techniques for LUAD, including palliative surgery, radiotherapy, chemotherapy, and immunotherapy, the prognosis for LUAD patients is still not good, with a 5-year survival rate of only (Taylor JA., et al 2003). The negative effects of these treatments are also frequently severe, diversified, and long-lasting, which makes them difficult for

patients to bear and makes them unavoidable (Brinkeborn RM., et al 1999). As molecular biology has developed quickly, molecular targeted therapy has emerged as a research hotspot and shown promising therapeutic results (Basuroy SA., et al 2006). Despite this, treatment resistance and individual differences make it difficult to cure LUAD patients (Bauer R., et al 1991). So, it is essential to look for an efficient Drug resistance and indifference (Melchart D., et al 1998). So, it is essential to look for an adjuvant therapy that is efficient and secure. For thousands of years, traditional Chinese medicine has been used in China to both prevent and treat cancer (Eisenberg DM., et al 1998). TCM is still a strong and indispensable choice for cancer adjuvant therapy today because to its effectiveness, few adverse effects, wide availability, and affordable cost (Grimm W., et al 1999). This is especially true for cancer patients who cannot accept western medicine. It has been demonstrated that bufalin, the main bioactive component of Bufonis Venenum that resembles digoxin, has a strong inhibitory effect on a variety of cancer types, including breast, bladder, ovarian, stomach, and liver cancers (Mullins RJ., et al 1998). Along with having exceptional anticancer properties, it can also increase heart contraction, control blood pressure, lessen discomfort, and reduce irritation, cough relief, and anaesthesia (Miller LG., et al 1998). As a result, it has recently attracted a lot of attention and in-depth inquiry. However, a scientific analysis of its effectiveness and mode of action against LUAD has not yet been conducted. To our understanding, bufalin shares the same multi-target and multi-pathway regulatory pharmacological properties as other TCM or TCM monomers, making it difficult to completely understand its treatment effects on LUAD using the traditional single target pharmacological paradigm. Luckily, this crucial gap has been bridged by the development of system biology, including network pharmacology and metabolomics. Network pharmacology, a dynamic and potent field, combines network biology, classical pharmacology, bioinformatics, chemical informatics, and TCM's idea of holism. Network pharmacology, which is the cutting-edge of TCM research, seeks to understand the intricate connection between from a comprehensive viewpoint, relationships between medications and targets, targets and diseases, as well as between diseases themselves. It has been utilised more frequently to determine the active components, explain the pharmacological processes, and understand the compatibility rule of TCM prescriptions.

DISCUSSION

The term "metabolomics" refers to a multidisciplinary approach that uses high-throughput and high-resolution detection technology along with pattern recognition analysis to qualitatively or quantitatively analyse all endogenous low-molecular-weight metabolites produced by a cell, tissue, or organism over a specific time period. Metabolomics is frequently used as a technique for understanding how cells and entire organisms function in health and disease because it offers interpretation of the complex relationships between the genotype and phenotype and mechanistic insights into the aetiology of many diseases. The putative pharmacological mechanisms of bufalin were investigated here. Network pharmacology, untargeted metabolomics, and molecular biology research were used to study LUAD. In the 2020 edition of the Chinese Pharmacopoeia, Heilongjiang Academy of Traditional Chinese medication has independently produced the Qifenggubiao granule, a new Chinese medication that combines the essence of Yupingfeng powder and Shengmai yin. In the treatment of allergic rhinitis, chronic cough, and other disorders, it exhibits impressive pharmacodynamic outcomes and conclusive clinical effects. It has an immunomodulatory impact, as demonstrated by prior pharmacological research, although the exact mechanism by which it modulates immunity is yet unknown. In this work, the immune hypofunction model was established in mice using cyclophosphamide, and the model was assessed using weight changes, the index of immune organs in the spleen and thymus, pathological sections of immune organs, and inflammatory factors. By combining the targets of blood components, metabolites, and diseases through network pharmacology, the prospective targets of Qifeng Gubiao Granule immunomodulation were obtained based on the metabolic biomarkers discovered by metabonomics technology. On the potential targets, GO enrichment analysis and KEGG pathway analysis were done. In addition to improving body weight and organ index, QFGBG can repair immunological organ damage brought on by CP. 13 metabolites with significant alterations were found by metabonomics, and the level of phospholipid metabolites in the model group was one of them. The model group had considerably higher levels of sphingosine -1- phosphate, palmitoyl phosphatidylcholine [LysoPC, and other metabolites. By intersecting 629 component targets, 202 metabolite targets, and 1916 disease targets, 98 targets of Qifeng's external immune control were found. The top 20 metabolic pathways mostly involved the IL-17 signalling pathway, TNF signalling pathway, Sphingolipid signalling pathway, and so on. KEGG pathway analysis found 233 linked metabolic processes. Through the Sphingolipid signalling pathway, QFGBG may affect AKT1, IL6, MAPK3, PTGS2, CASP3, MAPK1, ESR1, PPARG, HSP90AA1, PPARA, and other targets. The immunomodulatory impact of QFGBG was validated in combination with pharmacodynamic analysis, and the immunomodulatory mechanism of QFGBG with numerous targets and various routes was preliminary clarified. To narrow the target range of QFGBG immunomodulation, this study will combine metabonomics and network pharmacology methods. Metabonomics identifies potential biomarkers, and network pharmacology is used at the same time to find biomarker targets and correlate component targets and disease targets. The mice were weighed before modelling and after the experiment, and the weight changes of the mice in each group were measured. Mice in each group fasted for 12 hours following the last administration time.

CONCLUSION

Moreover, full blood was drawn; The serum was prepared by centrifuging 1 mL of whole blood at 3000 rpm and 4°C for 15 minutes. Spleen and thymus tissues from each group of mice were also taken, weighed, and then preserved in 4% neutral formaldehyde. After cleaning, the liver tissue was frozen. Differential Metabolite Targets Prediction Based on metabolomics, the acquired differential metabolites were entered into the Swiss Target Prediction database to obtain metabolite targets and the HMDB database to obtain the SMILE format of substances. The "metabolite-target" network diagram can be created by entering the target into Cytoscape 3.8.2. Important bodily immunological organs include the thymus and the spleen. The body's immunological health can be indicated by the size of the thymus index. According to the aforementioned findings, mice's immune systems are suppressed, and QFGBG has a specific impact on enhancing defences. One of the body's physiological processes is immunity. In order to preserve human health, the body depends on this ability to distinguish between "self" and "non-self" components. As a result, it can reject and eliminate antigens that enter the body as well as damaged and tumour cells that it has produced. The three primary roles of the immune system are defence, stabilisation, and surveillance. Pathological reactions will start to happen once these functions are out of balance.

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