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ORIGINAL ARTICLE

Combined Network Pharmacology and Cell Experiments to Explore the Anti-Inflammatory Mechanisms of Matrine

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ABSTRACT

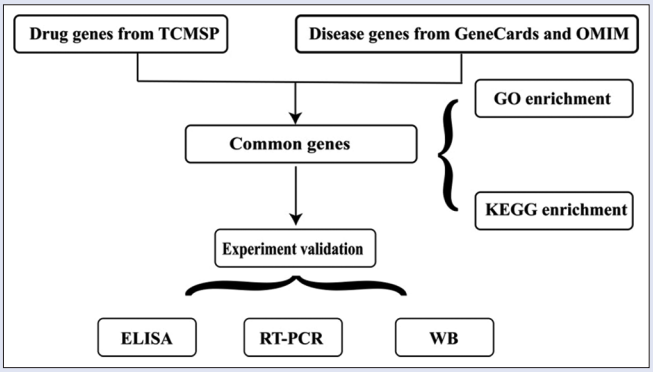
Background: Matrine is an alkaloid compound isolated from the root of *Sophorae Flavescentis Radix*. Despite being a potent anti-inflammatory agent, the underlying mechanisms of these anti-inflammatory properties have not been scrutinized. **Objectives:** To briefly elucidate the anti-inflammatory mechanism of matrine through network pharmacology and *in vitro* experiments. **Materials and Methods:** Multiple public databases analyzing targets associated with matrine and inflammation were surveyed. Thirty common targets acquired from the Venn diagram were used to compose the protein–protein interaction (PPI) network visualized by Cytoscape software for the subsequent analysis. **Results:** Network pharmacology revealed that 30 genes in matrine could interrupt the inflammatory metabolism to alleviate its development and progression. The cellular experiments revealed that matrine reduced the expression of interleukin-6 and tumornecrosis factor-α. **Conclusion:** Our results provide preliminary evidence and theoretical background regarding the role of matrine to assuage the inflammatory reaction, and support its future clinical application.

Key words: Anti-inflammation, data analysis, inflammatory immune, matrine, network pharmacology

SUMMARY

- Network pharmacology was helpful in drug development.

Abbreviations used: CS: Cigarette smoke, COPD: Chronic obstructive pulmonary disease, BALF: Bronchoalveolar lavage fluid; ALI: Acute lung injury; LPS: Lipopolysaccharide; DL: Drug-likeness; OB: Oral-bioavailability; CC: Cellular component; BP: Biological process; MF: Molecular function; PMA: Phorbol 12-myristate 13-acetate; RA: Rheumatoid arthritis



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INTRODUCTION

Inflammation is fundamental to different physiological and pathological procedures. The cause of inflammation can be multifaceted, such as the body's response to exoteric stimuli under the influence of biological, chemical, and physical factors, immune reaction and so on.[1] The recent coronavirus disease-2019 (COVID-19), which originated in Wuhan, China, disturbs the immune balance to cause a cytokine storm in some patients, which leads to a poor prognosis. It is also known that an exaggerated immune response is responsible for generating the cytokine storm even with an external stimulus.[2] Treatment with conventional drugs, such as steroids, lead to certain inevitable side effects, and widely using targeted drugs options is also challenging.[3] In this regard, traditional Chinese herbs may be a treasure in the development of modern medicine.

One such drug, matrine, is investigated widely for its anti-virus, anti-tumor, anti-inflammatory, and other diverse biological activities.[4-6] Cigarette smoke (CS) leads to amplified inflammatory and oxidative stress in the lungs, causing chronic obstructive pulmonary disease (COPD). It has been shown that matrine remarkably ameliorates CS-induced bronchoalveolar lavage fluid (BALF) and neutrophil elastase (NE) activity in mice, suggesting its therapeutic potential in COPD.[7] Another study revealed that matrine attenuated the inflammatory reaction in acute lung injury (ALI) caused by lipopolysaccharides (LPS), highlighting its potential as an alternative to glucocorticoid therapy for ALI.[8] A study published in 2014 reported that matrine is effective as an immunomodulatory natural product in the healing after encephalomyelitis by reversing the down-regulated expression of Nrf2 and HO-1 and inhibiting oxidative stress and inflammation in the central nervous system.[9]

Many studies have described that matrine could suppress inflammatory activity in a variety of diseases.[10,11] Therefore, it is only reasonable to devise methods to harvest the enormous anti-inflammatory potential of matrine to mitigate challenging inflammatory conditions, such

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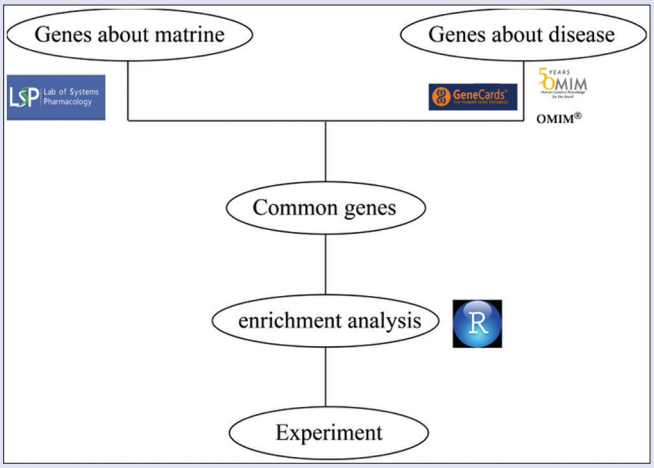

Figure 1: The work flow of this paper

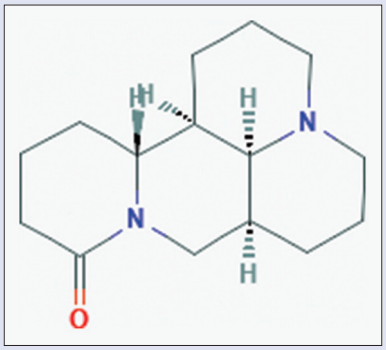

Figure 2: Structure of matrine (CAS number: 519-02-8). The red represents the oxygen atom. The blue represents the nitrogen atom. The gray represents the hydrogen atom. The rest of them were carbon skeleton

as in fever, wound healing. This study intends to combine network pharmacology with *in vitro* experiments to elucidate the mechanisms underlying matrine's anti-inflammatory properties to be used in clinical settings. The whole workflow was exhibited in Figure 1.

MATERIALS AND METHODS

Obtaining the anti-inflammation and inflammatory targets of matrine

Data regarding the physical and chemical properties of matrine were acquired from the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database (http://tcmspw.com).[12] The two parameters of drug-likeness (DL) and oral-bioavailability (OB) were vital for subsequent analysis and deep exploration. The chemical abstracts service (CAS) number was used to find matrine's 2D structure [Figure 2] quickly from the PubChem database (http://pubchem.ncbi).[13] We imported its formation data into the Swiss Target Prediction database (http://www.swisstargetprediction.ch) to look for its homologous targets, which are the predicted anti-inflammatory targets.[14]

Keywords related to "inflammation" were entered into the GeneCards (http://www.genecards.org/) and Online Mendelian Inheritance in Man (OMIM) databases (http://www.omim.org/) to obtain the disease targets.[15,16] The Uniprot database (http://www.uniprot.org/) is a comprehensive resource for protein sequences, which could be utilized for standardizing targets and acquiring gene symbols.[17]

Construction of a Protein–Protein Interaction network of common genes

The targets of inflammation and matrine were processed through the Draw Venn Diagram tool (http://bioinformatics.psb.ugent.be/webtools/Venn/). The results of the Venn analysis could attain common genes between matrine and inflammation, which represent the effective genes of matrine against inflammation. The STRING database (http://string-db.org/) could find the relationship in common genes between matrine and inflammation.[18] The default setting parameters were used; a TSV file was used for visualizing on Cytoscape (version 3.7.2).[19]

Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathway analysis

The Metascape dataset (http://metascape.org) provided specialized annotation for about 30 genes. The gene ontology (GO) analysis was used to determine the cellular component (CC), biological process (BP), and molecular function (MF) of the common genes.[20] A P value of <0.05 was considered statistically significant for GO enrichment. The Kyoto encyclopedia of genes and genomes (KEGG) enrichment analysis elucidated the distribution of these genes shown in the Venn diagram. The R software (version 4.0.1) was used to visualize the online-analyzed data.

Cell culture and stimulation

THP-1 cells were purchased from Genechem Enterprise (Shanghai, China). The cells were treated with RPIM 1640 (Gibico, USA) and 10% fetal bovine serum (Gibico, USA), 1% streptomycin, and penicillin (Gibico, USA) at 37°C in a cell incubator containing 5% CO_2. The logarithmic phase cells were pre-treated with Phorbol 12-myristate 13-acetate (PMA) (100 ng/mL, Sigma) for 24 h to become anchorage-dependent cells. Then, LPS (1 μg/mL, Sigma) was added to the cells for 24 h with or without matrine. In matrine given group, we set three different doses of matrine to interve the inflammation model, and the last dose of matrine (Shanghai, China) being 100, 200, 400 μg/mL, respectively, while the cells in the normal group were treated with RPIM 1640 alone. Under the pathophysiologic stimulation environment, monocyte is transformed into pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes. Separate differentiations of macrophages are vital for disease outcomes. It is known that THP-1 is the most frequently used cell to investigate the function of monocyte/macrophage *in vitro*.[21] PMA is applied as a differentiation drug, and LPS stimulates the differentiated THP-1 to synthesize and release diverse cytokines about inflammation.[22] Therefore, an inflammation cell model was built by PMA pre-treated THP-1 cell and combined with LPS.[23]

RNA isolation and Real-Time Polymerase Chain Reaction for gene expression

An real-time–polymerase chain reaction (RT–PCR) was performed to verify the effect of the matrine at the mRNA level. Total RNA extracted by the TRIzol reagent (Invitrogen, USA) was collected to synthesize the complementary DNA (cDNA). The SYBR Green PCR Master Mix (Applied Biosystems, USA) analysis was carried out to detect mRNA expression. Relative gene expression was calculated by the $2^{-\Delta\Delta Ct}$ method.[24] Table 1 presents the primers used in this study.

Enzyme-Linked Immunosorbent Assay

Cells were planted into a 24-hole plate in RPIM 1640 containing PMA. Cytokines are substances secreted from cells, and the supernatant of anchorage-dependent cells includes objective cytokines. The

Table 1: Real-Time PCR Primers

Gene	Forward primer (5′-3′)	Reverse primer (5′-3′)	Genbank Accession
IL-6	TCTACTCGGCAAACCTAGTGCGTTA	TTCTGACCACAGTGAGGAATGTCCA	NM_031168
TNF-α	GACCCTCACACTCAGATCATCTTCT	GCTACGACGTGGGCTACAG	NM_013693
β-actin	GTGTGACGTTGACATCCGTAAAGA	GCCGGACTCATCGTACTCCT	NM_007393.3

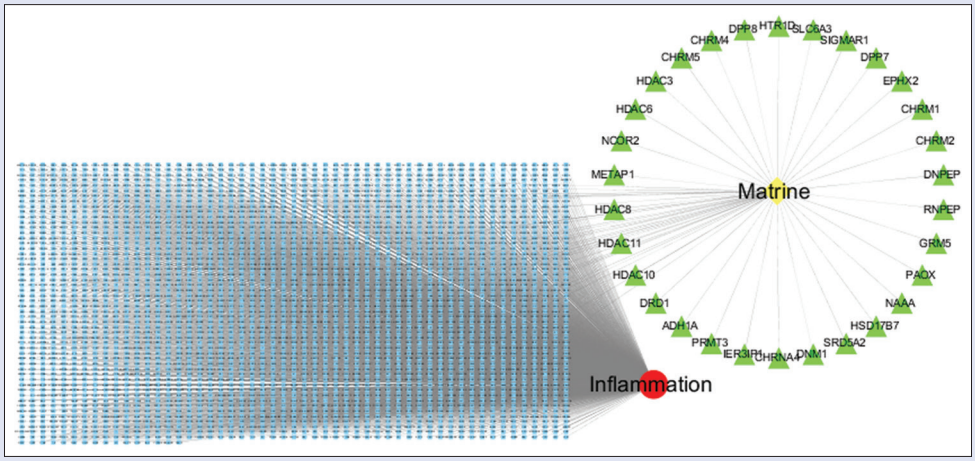

Figure 3: Drug–disease–gene symbol. Yellow diamandreprentsmatrine and green triangle represents 60 targets of matrine; red ellipse represents inflammation, and blue rectangle represents 2825 inflammation related targets

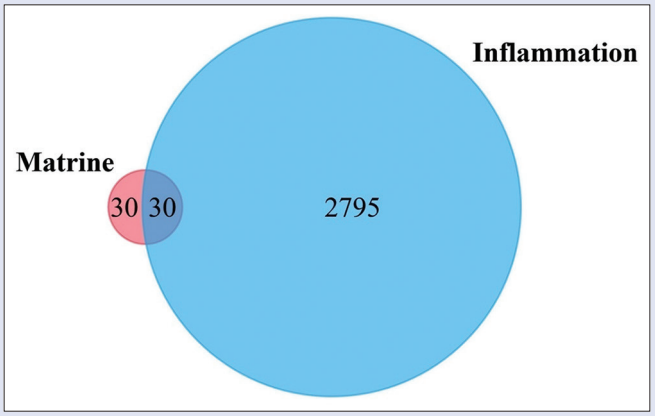

Figure 4: Sixty targets of matrine and 2825 targets of inflammation were analyzed by Draw Venn Diagram. The pink area represents the particular 30 genes in matrine, and the blue area represents the particular 2795 genes in inflammation. The overlapping district signifies the common genes in matrine and inflammation, which means effectual genes

supernatants in each group were collected and detected in enzyme-linked immunosorbent assay (ELISA) kits as per the manufacturer's instructions.

Western blot analysis

The THP-1 cells were split in Radio Immunoprecipitation Assay (RIPA) buffer adding phenylmethanesulfonyl fluoride (Biyotime, China). This step was carried out on the ice for dampening the protein exhaustion. After centrifugation at 4°C at 12000 rpm, the liquid supernatant was collected and quantified using a bicinchoninic acid (BCA) assay kit (Biyotime, China). An equal volume of protein was electrophoresed on sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) (Biyotime, China) for separating the proteins according to different molecular weights. The reference marker would transfer the desired belt to the polyvinylidene difluoride (PVDF) membrane (Biyotime, China). The non-specific antibody combined place was blocked with skimmed milk powder. Rabbit anti-human antibody of interleukin-6 (IL-6) and tumor-necrosis factor-α (TNF-α) (Abcam, UK) was dissolved in Tris-HCl and Tween-20 (TBST) (1:1000) as primary antibody. Then, HRP-conjugated secondary antibody (1:1000) combined with the first antibody. The protein bands were detected using enhanced chemiluminescence (ECL) Kit (Biyotime, China). The gray value of the target protein, normalized with the β-actin intensity, was quantified with Image J Software (version 1.52).

Statistical analysis

The data were presented as mean ± standard deviations (SD). We used one-way analysis of variance (ANOVA) to carry out the statistical analysis in the Statistical Package for the Social Sciences (SPSS version 18.0). A P value of <0.05 was considered statistically significant.

RESULTS

Characteristics of matrine in TCMSP

The criteria of OB ≥30% and DL ≥0.18 indicate the optimum availability value of a drug. The TCMSP database provides comprehensive parameters for diverse traditional drugs. Via database screening, the DL and OB of matrine were 0.25 and 63.77, respectively, which satisfies the aforementioned criteria.

The acquisition of common genes between matrine and inflammation

As shown in Figure 3, 60 targets of matrine and 2825 associated with inflammation were obtained from the Swiss Target Prediction, and Gene Cards and OMIM databases, respectively [Figure 3]. The Venn diagram showed that there were 30 overlapping genes, which represent the

potential effective genes of matrine against inflammation on comparing the genes between matrine and inflammation [Figure 4].

Construction of a PPI network of matrine countering with inflammation

Protein–protein interaction (PPI) network is constituted by nodes and edges. Nodes stand for genes about matrine against inflammation, and edges between various nodes indicate the interaction of separate genes. Thirty common genes screened by the Venn diagram were observed in the PPI network, in which there were 193 edges [Figure 5].

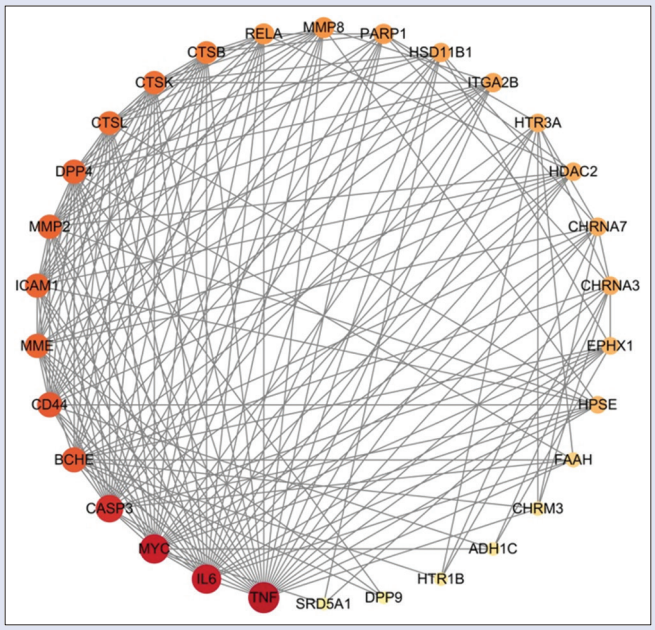

Figure 5: PPI network of 30 common genes. Color and volume change indicate the importance of nodes in PPI. The darker and bigger dots represent more vital genes

As evident from the PPI, we noticed that with decreasing significance of nodes, the color of the dots became lighter and the size became smaller.

GO enrichment and pathway analysis

The 30 genes of matrine against inflammation were submitted to Metascape for enrichment analysis. Ten items of BP, CC, and MF were singled out to draw bar plots, according to the count number [Figure 6].

The KEGG results showed that the 30 genes were enriched in 48 signaling pathways. High-related pathways were exhibited through R software, including apoptosis, TNF-signaling pathway, NF-kappa-B signaling pathway, toll-like receptor signaling pathway, and so on [Figure 7].

Anti-inflammatory effect of matrine

The results of RT–PCR demonstrated that the expression of IL-6 and TNF-α increased in the model group compared with the normal group, while groups with matrine exhibited competence to regulate the IL-6 and TNF-α levels. Matrine inhibited the inflammation in a dose-dependent manner, generally on gene level [Figure 8]. The protein level experiments showed that matrineimpedesIL-6 and TNF-α expression in modeling with 200 and 400 μg/mL of matrine doses. However, the predicted decreased protein expression of IL-6 and TNF-α in the group receiving 100 μg/mL matrine did not exhibit statistical significance in the western blotting experiment, while the phenomenon was noted in ELISA [Figures 9 and 10].

DISCUSSION

Inflammation is associated with a sundry of malignant diseases, such as heart failure, and metabolic cardiomyopathy.[25] Cardiomyocytes immersed in a variety of cytokines and inflammation mediators undergo hypertrophy, apoptosis, eventually leading to unavoidable cardiac remodeling.[26] Inflammation is also often linked to the development and progression of cancer. An immunosuppressive environment composed of extrinsic and intrinsic inflammation activity can facilitate tumor growth and metabolism.[27] Hence, anti-inflammatory strategies are becoming a hot spot in modern medicine to treat various inflammatory diseases. Some studies have reported that matrine diminishes the abundance of

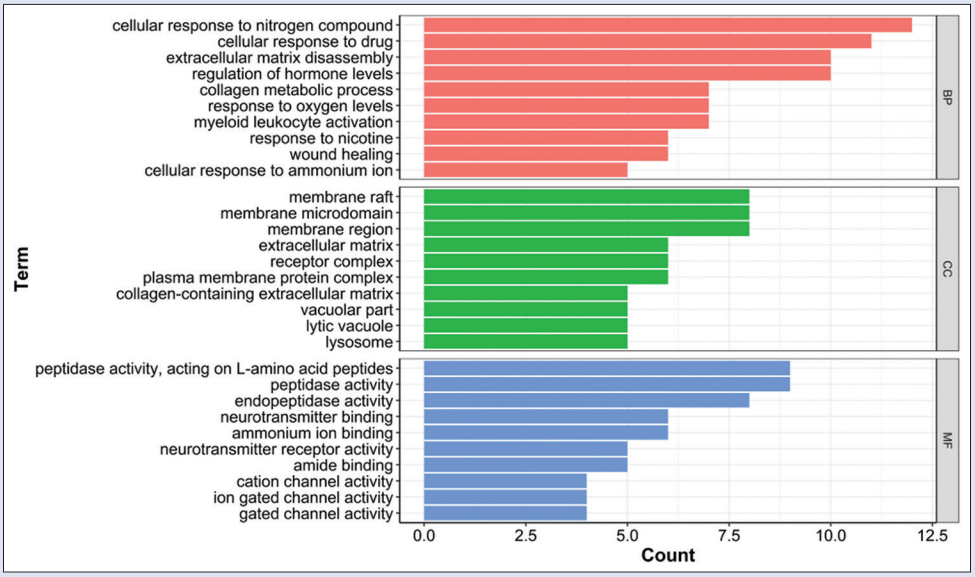

Figure 6: GO analysis for 30 common genes. Red column represents the biological process of 30 genes. Green column represents the cellular components of 30 genes. Blue column represents the molecular function of 30 genes

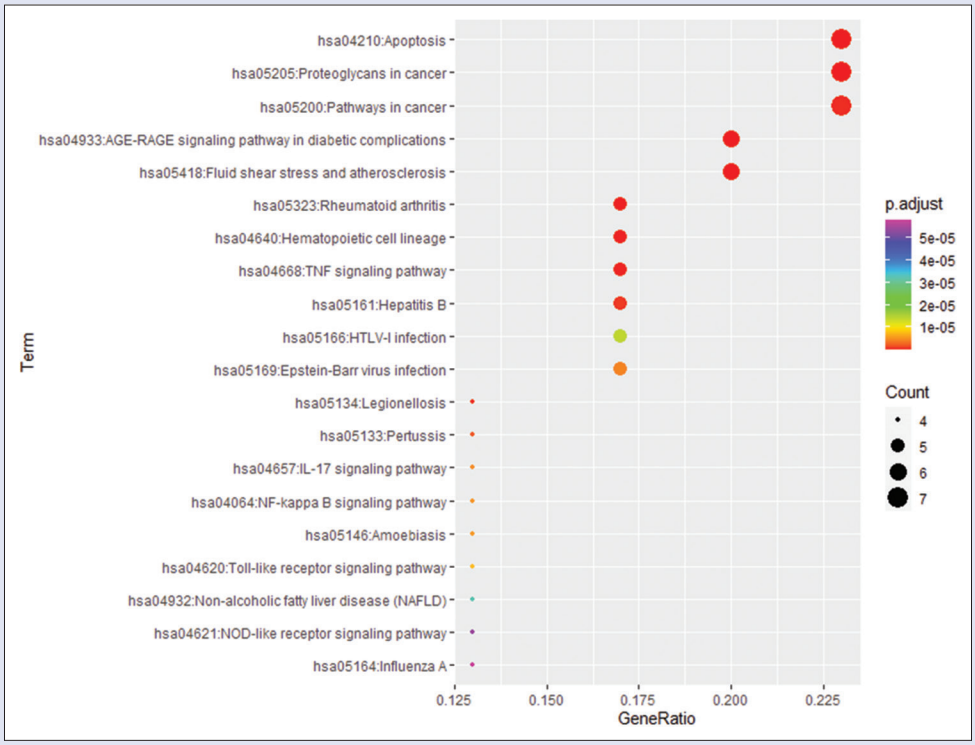

Figure 7: KEGG results of 30 common genes. The bubble plot was drawn by R software. The rainbow color represents the adjusted *P* value, and the size of spots represents genes number enriched in the different pathways

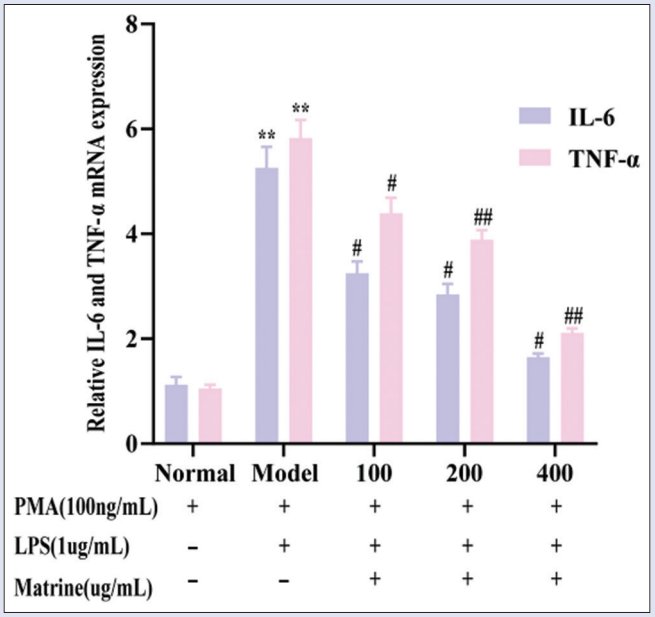

Figure 8: Effect of matrine on the mRNA expression of TNF-α and IL-6. After stimulating by LPS (1 μg/mL) for 24 h, the gene expression of IL-6 and TNF-α was increased, while matrine declined the up-regulated level in drug-given group. $^{**}P < 0.01$ versus normal group, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ versus model group. The data were represented as the mean ± SD of three independent experiments

M1 macrophages in the tumor area, exerting a benign effect on colorectal cancer and liver cancer via inducing apoptosis.[28,29] In a virus co-infected mouse model, matrine directly inhibited virus replication and increased the proliferation activity of lymphocytes, elucidating its ability for immune recovery.[30] Immune homeostasis depends largely on the balance of T helper 1 and T helper 2 (Th1 and Th2), and dysequilibrium observed in diverse autoimmune diseases, such as rheumatoid arthritis (RA). It has been observed that matrine restrained the over-expression of Th1 cytokine, TNF-α, and IL-1β in an RA model.[31] Therefore, the use of artificial technology in modern medicine may help in digital mining to determine more useful information about matrine.

Network pharmacology is a widely employed strategy of artificial intelligence to evaluate the association between drugs and disease, and network-based approaches are expected to highlight this from underneath multiple layers of information.[32] Absorption, distribution, metabolism, and excretion (ADME) properties and certain drug physical parameters can be used to assess the value of an ideal drug. Therefore, the evaluation of ADME characters holds great significance in drug employment to accelerate the drug discovery process.[33] DL is a parameter designed to appraise the potential of a component to develop into a drug; DL ≥0.18 is used for selecting the desired components in pharmaceutics. Likewise, an OB value of 30% reflects the drug availability; high absorption means the drug may wield an increasing number of metabolites while exerting its curative function.[34] Matrine satisfied both the criteria, OB ≥30% and DL ≥0.18, implying its possible exploitation to yield a useful drug.

Target prediction helps in determining the corresponding genes of components. In our study, we identified 30 anti-inflammatory genes for matrine via a computer algorithm. Furthermore, the PPI network analysis also exhibited the 30 common genes between matrine and inflammation, which were considered as effective genes for the next analysis. These genes evoke further interest to improve the link between drugs and disorders. Combined with the PPI and KEGG results, we found that the inflammation-related pathways, such as the NF-κB, toll-like receptor, and TNF signaling pathways, included the two most

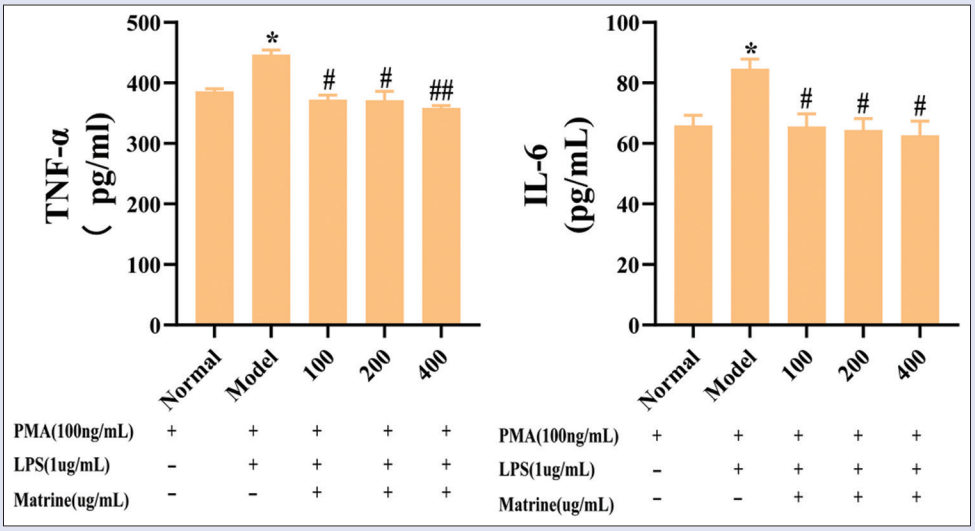

Figure 9: Effect of matrine on the cytokine expression of TNF-α and IL-6. After stimulating by LPS (1 μg/mL) for 24 h, the cytokine expression of IL-6 and TNF-α was increased, while matrine declined the up-regulated level in drug group. **P* < 0.05 versus normal group, #*P* < 0.05, ##*P* < 0.01 versus model group. The data were represented as the mean ± SD of three independent experiments

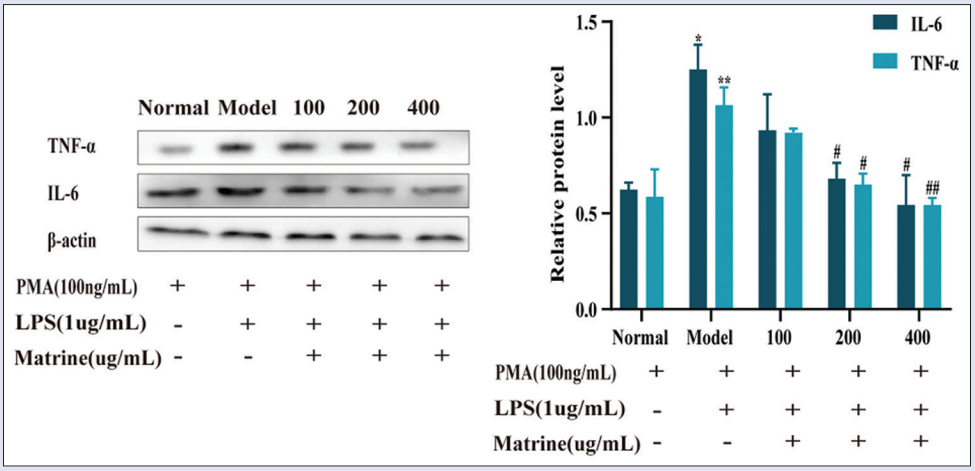

Figure 10: Effect of matrine on the protein expression of TNF-α and IL-6. After stimulating by LPS (1 μg/mL) for 24 h, the protein expression of IL-6 and TNF-α was increased, while matrine-given group declined the up-regulated level of IL-6 and TNF-α at 200 and 400 μg/mL. All values were expressed as mean ± SD. **P* < 0.05 versus normal group, #*P* < 0.05, ##*P* < 0.01 versus model group. The data were represented as the mean ± SD of three independent experiments

important genes, IL-6 and TNF. Therefore, IL-6 and TNF were chosen for the next verification. The interleukin family of cytokines consists of IL-6, IL-11, IL-27, and other components; a distortion of inflammatory cytokines promotes the disease progression into deterioration.[35] Whenever there are infections or tissue injuries, the secreted IL-6 is partly responsible for the elimination of infectious agents through the activation of an immune response.[36] Furthermore, a study reported that the increased levels of IL-6 in porcine alveolar macrophages (PAMs) were down-regulated by matrine through the NF-κB pathway.[37] TNF is a cytokine divided into TNF-α and TNF-β according to different cell sources. TNF-α is mainly produced by activated macrophages and is functionally comparable to IL-6. In colorectal cancer, matrine reduced the levels of enriched IL-6 and TNF-α, exhibiting its strong competency to repress the inflammation in cancer.[38] TNF-α participates in oxidative stress, which is a significant process during inflammation, and low-dose TNF-α production may accelerate tumor growth.[39] Consequently, timely elimination of adverse inflammation is of great significance.

The RT-PCR, ELISA, and Western blotting analyses exhibited that matrine inhibited the exaggerated production of IL-6 and TNF-α at mRNA and protein levels. The shift between model and matrine groups signifies that matrine inhibits the elevated levels of IL-6 and TNF-α, exhibiting its anti-inflammatory power. These results are in line with previous research in this field.[40,41]

Large-scale data needs a computational algorithm to dig out constructive information quickly. In this paper, we found some core genes in matrine against inflammation using artificial intelligence. The cell experiments further confirmed these outcomes of algorithmic calculations, suggesting that network pharmacology may play an important role in drug effect verification and drug discovery.[42] However, the information loss during this process warrants great attention. The degree of vertices omitted during monopartite projection is the major determinant of information loss.[43] Thus, strategies to appropriately deal with the problem of information loss during analysis may be explored in future studies. Nevertheless, this paper briefly introduced the mechanisms

through which matrine acts against inflammation. Also, the effective genes identified in matrine, as calculated by computer algorithms, can greatly impact the inflammatory process.

CONCLUSION

The present work combined network pharmacology and experimental validation to elucidate matrine's mechanism of action against inflammation and the potential functional targets. It signifies that network pharmacology may be a useful strategy to determine drugs targets.

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Conflicts of interest

There are no conflicts of interest.

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