**ORIGINAL RESEARCH ARTICLE**

# Multi-target mechanism of misoprostol in pregnancy termination based on network pharmacology and molecular docking

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*Rui Zhang#, Jing Cao#, Lanlan Li, Yurong Zhu, Wei Dai, Tao Yang and Yaguang Hu**

Department of Pharmacy, Gansu Provincial Maternity and Child-care Hospital, Lanzhou, China

***For Correspondence:** Email: *huyaguang_pharm@163.com*; Phone: +86 0931 6968657
# Both authors are co-first authors and have contributed equally to this work

## Abstract

Misoprostol is a prostaglandin analogue that contracts the uterus, prompting the expulsion of the embryo. No systematic evaluation of the mechanisms of misoprostol has previously been performed. In this study, known targets of misoprostol were obtained from the DrugBank database; potential targets of misoprostol were predicted using data from the SwissTargetPrediction and PharmMapper databases; and the main targets of pregnancy termination were obtained from the GeneCards database. The protein–protein interaction (PPI) network of the shared genes between misoprostol and pregnancy termination was constructed using data from the STRING database, and the "misoprostol–pregnancy termination–pathway" network was constructed and potential targets was verified through molecular docking. We analyzed 37 shared target genes and obtained a network diagram of 134 potential targets, which the core therapeutic targets were HSP90AA1, EGFR, and MAPK1. GO functional and KEGG pathway enrichment analyses showed that misoprostol can modulate the VEGF signaling pathway, calcium signaling pathway, and NF-κB signaling pathway in pregnancy termination and mainly interferes with protein phosphorylation, cell localization, and protein hydrolysis regulation processes. This research illustrates the mechanism underlying the pharmacological effect of misoprostol, namely pregnancy termination. However, further experimental verification is warranted for optimal use of misoprostol during clinical practice. *(Afr J Reprod Health 2024; 28 [3]: 114-121)*

**Keywords:** Misoprostol, pregnancy termination, network pharmacology, multi-target mechanism

## Résumé

Le misoprostol est un analogue des prostaglandines qui contracte l'utérus, provoquant l'expulsion de l'embryon. Aucune évaluation systématique des mécanismes du misoprostol n'a été réalisée auparavant. Dans cette étude, les cibles connues du misoprostol ont été obtenues à partir de la base de données DrugBank ; Les cibles potentielles du misoprostol ont été prédites à l'aide des données des bases de données SwissTargetPrediction et PharmMapper ; et les principales cibles de l'interruption de grossesse ont été obtenues à partir de la base de données GeneCards. Le réseau d'interaction protéine-protéine (IPP) des gènes partagés entre le misoprostol et l'interruption de grossesse a été construit à l'aide des données de la base de données STRING, et le réseau « voie d'interruption de grossesse-misoprostol » a été construit et les cibles potentielles ont été vérifiées par amarrage moléculaire. Nous avons analysé 37 gènes cibles partagés et obtenu un diagramme de réseau de 134 cibles potentielles, dont les principales cibles thérapeutiques étaient HSP90AA1, EGFR et MAPK1. Les analyses d'enrichissement des voies fonctionnelles GO et KEGG ont montré que le misoprostol peut moduler la voie de signalisation VEGF, la voie de signalisation du calcium et la voie de signalisation NF-κB lors de l'interruption de grossesse et interfère principalement avec les processus de phosphorylation des protéines, de localisation cellulaire et de régulation de l'hydrolyse des protéines. Cette recherche illustre le mécanisme sous-jacent à l'effet pharmacologique du misoprostol, à savoir l'interruption de grossesse. Cependant, une vérification expérimentale plus approfondie est justifiée pour une utilisation optimale du misoprostol au cours de la pratique clinique. *(Afr J Reprod Health 2024; 28 [3]: 114-121).*

**Mots-clés**: Misoprostol, interruption de grossesse, pharmacologie de réseau, mécanisme multi-cibles

## Introduction

Induction of labor occurs in approximately 20% of pregnancies for a variety of reasons[1]. Pregnancy termination can be performed surgically, such as with negative pressure suction, or using abortion medications. At present, mifepristone and misoprostol are the main drugs used for the clinical termination of pregnancy. Mifepristone is a steroid antiprogesterone preparation, which can cause degeneration and necrosis of uterine decidua and cervical softening[2]. Misoprostol is a prostaglandin analogue that contracts the uterus, prompting the expulsion of the embryo.

Misoprostol increases uterine pressure by increasing uterine smooth muscle tone, thus leading

to uterine contraction and abortion. It also has the effect of promoting cervical maturation and softening[3]. Preliminary outcomes of the use of misoprostol suggest that oral misoprostol tablets at 200 μg per dose may improve outcomes in pregnancy termination and be cost-saving[4]. Additionally, a large number of clinical trials have shown that misoprostol is effective in the termination of second-trimester pregnancy, termination of stillbirths, third-trimester labor induction, and the prevention of postpartum hemorrhage[5-8]. Misoprostol can effectively promote cervical maturation, and has the advantages of low price, easy storage and long action time, which make it an ideal drug for inducing labor. However, its mechanism of action is still unclear.

Based on the "disease–gene–target–drug" interaction network, network pharmacology involves systematically and comprehensively observing the influence of drugs on the disease network to uncover the origin of drug synergism in the human body. Network pharmacology reflects the new trend of systematic research in biomedicine in the era of big data and answers the urgent need for systematic research methods. Molecular docking is a method to design drugs by directly analyzing the characteristics of receptors and the interaction between receptors and drug molecules. This theoretical simulation method is used to study molecular interactions, such as ligand–receptor interactions, and predict binding patterns and affinities. In recent years, it has become an important technique in the field of computer-aided drug research[9-10]. Based on network pharmacology and molecular docking, we aimed in this study to predict the mechanism of pregnancy termination by misoprostol so as to provide a theoretical basis for the use of misoprostol in pregnancy termination.

# Methods

### *Screening of misoprostol - related targets*

Misoprostol's simplified molecular-input line-entry system(SMILES) information and its 2D structure were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The 2D structure was uploaded to the PharmMapper database (http://www.lilab-ecust.cn/pharmmapper/), and the SMILES information was uploaded to the Swiss Target Prediction database (http://www.swisstargetprediction.ch/) to predict the potential targets of misoprostol. The DrugBank database (https://go.drugbank.com/) was used to identify known misoprostol targets. Misoprostol-related target information was obtained by merging the target information from the three databases and deleting duplicate values. All retrieved targets were normalized using the UniProt database (https://www.uniprot.org/).

### *Screening of targets related to pregnancy termination*

"Termination of pregnancy" was selected as keyword to dig potential targets in GeneCards (https://www.genecards.org/), in which the higher the score represents the target with disease linked more closely. Duplicates were removed from the data and then collated to obtain targets related to termination of pregnancy. "Misoprostol - termination of pregnancy" common targets were obtained by using Venn Diagram (http://bioinformatics.psb.ugent.be/webtools/Venn/)

### *Construction and network topology analysis of protein-protein interaction network (PPI) targeted by Misoprostol and pregnancy termination*

Setting the species to Homo sapiens and the interaction confidence score to 0.7, defined as high confidence on the Interaction Gene Retrieval Tool (STRING) platform (https://string-db.org/), protein–protein interaction (PPI) data were obtained from STRING. The misoprostol–pregnancy termination PPI network was constructed using Cytoscape 3.9.0 software, and the network topology was analyzed according to the intersection network.This study evaluates the criticality of nodes in the whole network based on the parameters of Degree, Betweeness centrality and Closeness centrality.closeness centrality.If there is a regulatory relationship between nodes in the network, and are connected by an edge.

### *Screening of pivotal target proteins and Gene Onotology/Kyoto Encyclopedia of Genes and Genomes(GO/KEGG) analysis*

To illustrate the potential function of the genes targeted by the therapeutics and the role of signaling

pathways, the targets of pregnancy termination caused by misoprostol were entered into the Metascape platform (http://metascape.org/gp/index.html). Gene Ontology (GO) functional and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were then performed. The main objects of GO functional enrichment analysis were biological processes, molecular functions, and cellular components. The species was set to "sapiens" and the significance was set to $P < 0.01$ to analyze the main biological processes and metabolic pathways. The results of enrichment analysis were then visualized. Each KEGG pathway category was obtained from the KEGG Pathway database (https://www.kegg.jp/kegg/pathway.html) for further analysis. Cytoscape 3.9.0 software was used to construct the "active ingredient–target–pathway" network using the built-in tool, and then the drug, target, and pathway flag sizes were set according to the degree value. The network diagram of "misoprostol–common target–pathway" was then constructed.

### *Molecular docking*

The crystal structure of the protein receptor was obtained from the RCSB Protein Database (http://www.rcsb.org/). The downloaded protein structures were pretreated with PyMol 2.4.0 to remove the original ligands, solvent molecules, and redundant protein chains and add polar hydrogens. AutoDock Tools 1.5.6 was then used to calculate the Gasteiger charges and determine the center and dimensions of the docking box. The 3D structure of misoprostol was treated by polar hydrogenation and energy minimization using the MMFF94s force field. Misoprostol binding and the central targets were assessed by molecular docking using AutoDock Vina. Prior to molecular docking, all protein and misoprostol structures were converted to PDBQT format using AutoDock Tools 1.5.6. Then, AutoDock Vina was used to dock misoprostol to the protein. Finally, the binding affinity calculated by AutoDock Vina was recorded, and the docking results were visualized by PyMol 2.4.0.

## Results

### *Misoprostol - Target network*

A total of 110 misoprostol targets were obtained after removing duplicates from the DrugBank and SwissTargetPrediction databases. These included four known targets (accounting for 3.6% of the total targets) and 106 predicted targets (96.4% of the total). In addition, there were four cross-targets between the known targets and potential targets. Then, the misoprostol–target network was constructed using Cytoscape 3.9.0 (Figure 1A).

### *Screening and analyzing the genes shared by misoprostol and pregnancy termination as well as performing network analysis*

A total of 1,860 targets related to pregnancy termination were screened from the GeneCards database, and a PPI network was constructed to demonstrate the interactions between pregnancy termination-related targets. Based on the medians of Degree, Betweeness centrality and Closeness centrality, which were 8, 0.00029114, and 0.29085283, respectively, 513 significantly related targets were obtained. The Venn diagram was used to identify the intersection of the selected misoprostol targets and pregnancy termination-related targets, and 37 common targets between misoprostol and pregnancy termination were obtained (Figure 1B).

The common targets obtained above were imported into the STRING database, and a PPI interaction network with 34 nodes and 127 edges was constructed using Cytoscape 3.9.0 and saved in TSV format (Figure 1C). Using Cytoscape's Network Analyzer tool to analyze the topological properties of the nodes in the network, it was found that the medians of degree of freedom, betweenness centrality, and closeness centrality were 7, 0.0165875, and 0.46478873. The 11 genes that exceeded the median of the degree of Degree, Betweeness centrality and Closeness centrality were selected as core genes (Table 1).

The common targets and pathways of drugs and diseases were used to construct the network

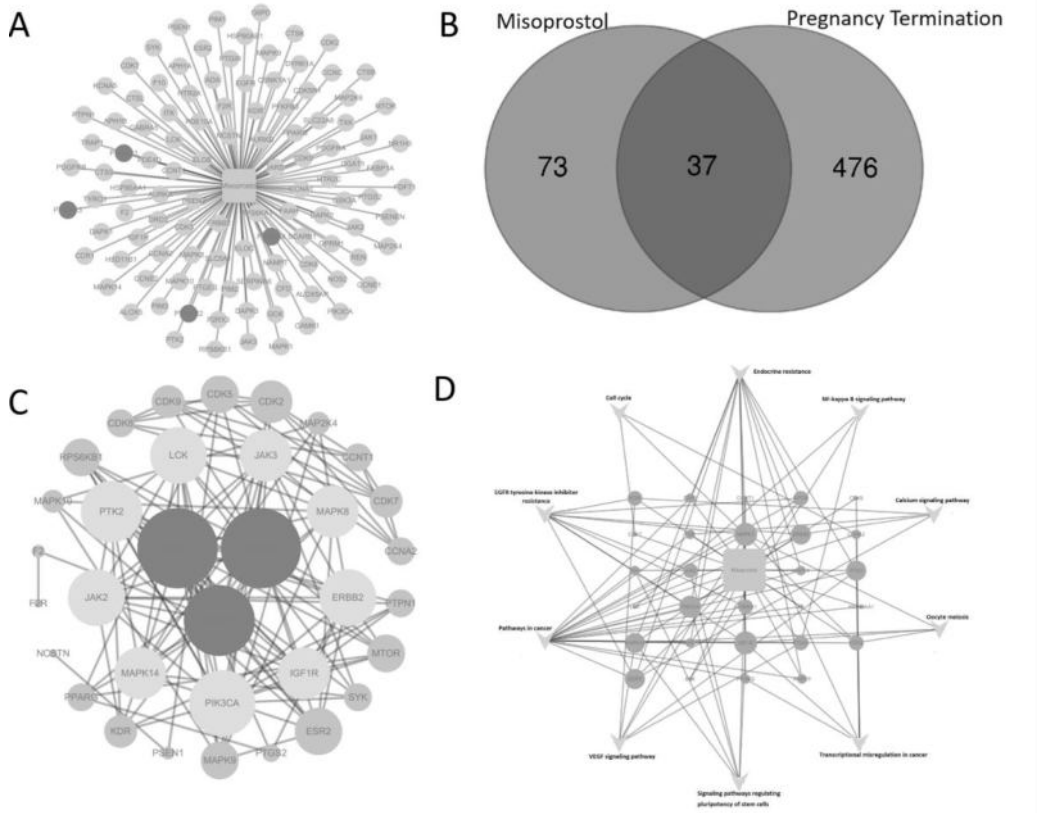


**Figure 1.** Network pharmacology on Misoprostol-pregnancy termination**. Figure 1A.** Misoprostol - target network. Green denotes predicted targets, red denotes known targets and cross targets. **Figure 1B.** Venn diagram of targets associated with Misoprostol -pregnancy termination. **Figure 1C.** PPI network of misoprostol -pregnancy termination targets. The size of the node varies from orange to green in color according to the degree of freedom value, and the nodes are arranged in descending order from inside to outside. The larger the node is, the more important the node is in the network. **Figure 1D.** Misoprostol - common target - pathway PPI network. Square nodes represent misoprostol, circular nodes represent common targets, and triangular nodes represent pathways.

**Table 1:** Basic information on key targets

| Targets | Proteins | BC | CC | DC |
|---|---|---|---|---|
| HSP90AA1 | Heat Shock Protein 90 Alpha Family Class A Member 1 | 0.28439955 | 0.62264151 | 16 |
| EGFR | Epidermal Growth Factor Receptor | 0.23233485 | 0.6 | 16 |
| MAPK1 | Mitogen-Activated Protein Kinase 1 | 0.08643959 | 0.56896552 | 14 |
| PIK3CA | PI3-kinase p110-alpha subunit | 0.02515355 | 0.52380952 | 13 |
| PTK2 | Protein Tyrosine Kinase 2 | 0.03174493 | 0.52380952 | 12 |
| LCK | Tyrosine-protein kinase LCK | 0.02593233 | 0.50769231 | 11 |
| ERBB2 | Erb-B2 Receptor Tyrosine Kinase 2 | 0.03273245 | 0.50769231 | 11 |
| MAPK14 | Mitogen-Activated Protein Kinase 14 | 0.05147844 | 0.50769231 | 10 |
| MAPK8 | Mitogen-Activated Protein Kinase 8 | 0.13014259 | 0.5 | 10 |
| JAK3 | Janus Kinase 3 | 0.04262229 | 0.48529412 | 10 |
| ESR2 | Estrogen Receptor 2 | 0.042 | 0.48529412 | 9 |

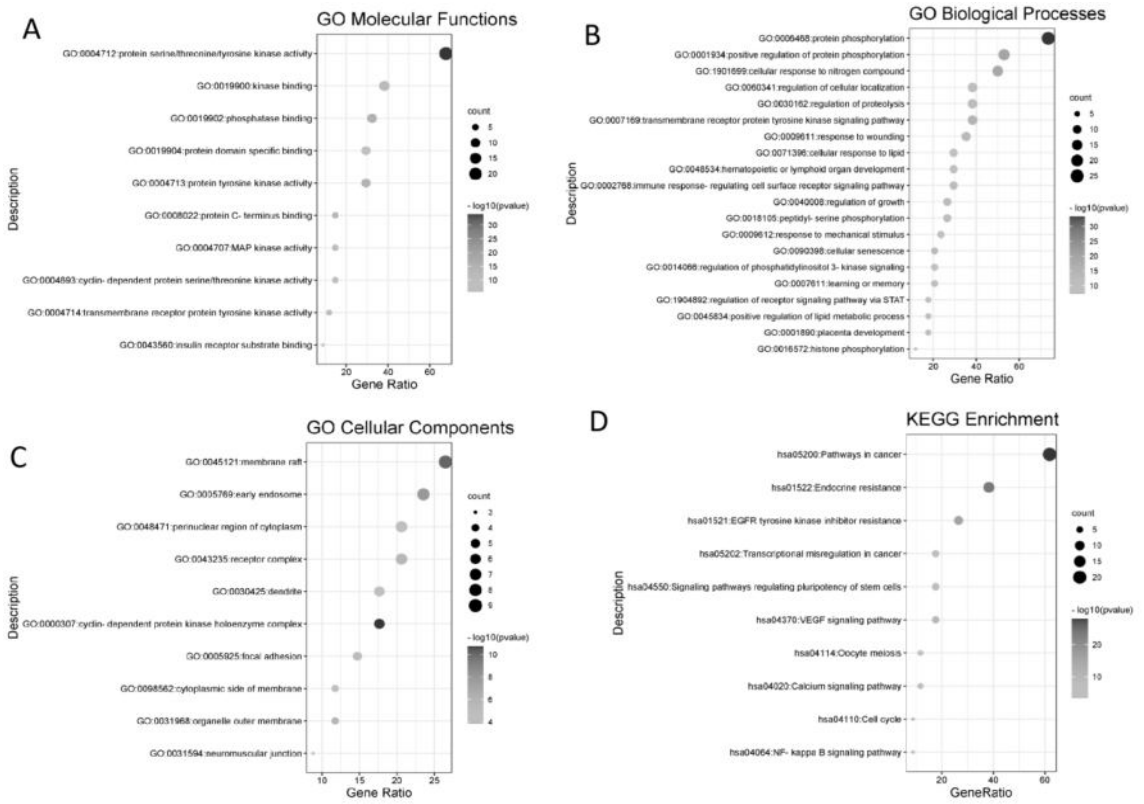


**Figure 2:** GO and KEGG enrichment analysis. (A) GO Molecular Functions, (B) GO Biological Processes, (C) GO Cell Components, (D) KEGG Enrichment Analysis

**Table 2:** Binding energy of Misoprostol to core target molecules

| Targets | PDBID | Binding Energy (kcal•mol-1) |
|---|---|---|
| EGFR | 1M14 | -5.9 |
| HSP90AA1 | 8B7I | -5.9 |
| MAPK1 | 4FUX | -5.5 |

diagram of "misoprostol–common target–pathway"(Figure 1D), in which the size of the nodes indicates their importance. The interaction network included 28 drug–disease common targets, 10 KEGG signaling pathways, 39 nodes, and 102 edges.

## *GO and KEEG enrichment analysis*

GO functional and KEGG enrichment analyses of 134 human genes that may be involved in the treatment of pregnancy termination with misoprostol were performed. The GO cellular components were mainly located in the membrane raft, early endosome, perinuclear region of cytoplasm, receptor complex, and cyclin-dependent protein kinase holoenzyme complex. The main GO molecular functions were related to protein serine/threonine/tyrosine kinase activity, kinase binding, phosphatase binding, protein domain-specific binding, and protein tyrosine kinase activity. The main GO biological processes were protein phosphorylation, positive regulation of protein phosphorylation, cellular response to nitrogen compounds, regulation of cellular localization, regulation of proteolysis, and the transmembrane receptor protein tyrosine kinase signaling pathway. KEGG enrichment analysis revealed that the proteins encoded by these genes were mainly involved in pathways of cancer, endocrine resistance, tyrosine kinase inhibitor resistance, and transcriptional misregulation in cancer and signaling pathways regulating pluripotency of stem cells (Figure 2).

## *Molecular docking*

We screened the targets for molecular docking with misoprostol. The binding strength and activity were

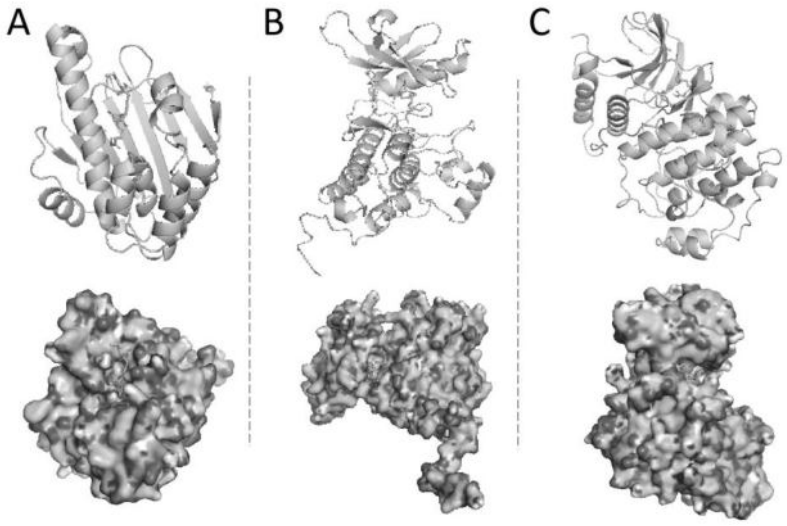


**Figure 3:** Molecular docking of misoprostol binding to its predicted protein targets. (A) HSP90AA1, (B) EGFR, (C) MAPK1

evaluated according to the binding energy and the number of hydrogen bonds generated. The lower the binding energy and the greater the number of hydrogen bonds, the more stable the binding conformation and the higher the binding activity between the receptor protein and target small-molecule ligands. Scores below -5 are considered to have the strongest docking capabilities. HSP90AA1, EGFR, and MAPK1 were found to constitute the most likely multi-target mechanism of misoprostol in pregnancy termination. The molecular docking results is shown in Table 2 and Figure 3.

## Discussion

In this study, the potential mechanism of misoprostol-induced termination of pregnancy at the level of the "active ingredient–drug target–pathway" was investigated by network pharmacology. This emerging interdisciplinary method involves a systematic combination of a variety of programs, based on the theory of systemic biology, using bioinformatics and network analysis methods to analyze biological systems at the system level to study drug mechanisms and multi-target drug molecular design[11].

The prostaglandin E1 analogue misoprostol is commonly used as a uterine dilator and cervix ripening agent[12]. Misoprostol alone is a safe and effective option for terminating second-trimester pregnancies[13]. According to the PPI network analysis diagram obtained in this study, misoprostol induces pregnancy termination through multiple targets and signal pathways, among which there are synergistic effects. The network diagram not only intuitively reflects the characteristics of misoprostol's pregnancy-terminating mechanism through multiple targets and routes but also shows that misoprostol is closely related to pregnancy termination targets. HSP90 plays fundamental roles in many cellular processes to maintain homeostasis, including cell proliferation, differentiation, and apoptosis. The molecular chaperone HSP90AA1 is a key regulator in various cellular processes under a variety of physiological and pathological conditions. It functions primarily by interacting with substrate proteins and promoting their folding and activity[14]. HSP90 protein expression can be readily detected in the cytoplasm of myometrial cells throughout pregnancy and the postpartum period in rats, and significant expression of HSP90 protein suggests that it plays a role in the proliferative phase of myometrium programming[15]. Epidermal growth factor (EGF) plays an important role in pregnancy maintenance and embryo and fetal growth and development by binding to its receptor, EGFR-1. Both EGF and EGFR-1 can be detected in the human placenta, endometrial tissue, and glandular secretions. EGF is an effective trophoblast-proliferating mitogen and can stimulate trophoblast

invasion. EGFR-1 is produced early in pregnancy by cells in the proximal part of the trophoblast column. The coordinating role of EGFR is essential for the successful progression of early pregnancy. In the absence of EGFR, more than 3,000 genes are misregulated. During implantation, disruption of the balance between activation and inhibition of regulatory factors that control immunity may lead to the accumulation of potentially cytotoxic decidual macrophages and Tregs that trigger immune-mediated abortion[16]. One study found that LncRNA-TCL6 was more highly expressed in placental tissues in cases of threatened abortion pregnancy than in those of normal pregnancy, suggesting that LncRNA-TCL6 promotes early abortion and inhibits placental implantation via the EGFR pathway[17]. Activated MAPK1 has been shown to regulate a number of cellular functions, including inflammation. MAPK1 regulates the release of LPs-stimulated proinflammatory cytokines and prostaglandins from the human placenta and fetal membranes. LncRNA HCG27 promotes glucose uptake by miR-378a-3p/MAPK1 pathway, which may provide potential therapeutic targets for gestational diabetes mellitus[18]. In addition, MAPK1 was found to be involved in IL1B-induced matrix metallopeptidase 9 (MMP9) mRNA and premMP9 gene expression in human primary amniotic cells[19].

To further analyze the signaling pathways and biological processes involved in misoprostol-induced pregnancy termination, this study conducted enrichment analysis of the KEGG signaling pathways and GO biological processes for pregnancy termination targets, identifying multiple KEGG pathways of the genes central to misoprostol-induced pregnancy termination. These pathways are mainly involved in endocrine resistance, EGFR tyrosine kinase inhibitor resistance, transcriptional misregulation, signaling pathways regulating pluripotency of stem cells, the VEGF signaling pathway, calcium signaling pathway, NF-κB signaling pathway, and others. It was previously found that the VEGF signaling pathway[20], NF-κB signaling pathway[21], and calcium signaling pathway[22] were involved in pregnancy termination. This suggests that misoprostol plays a role in pregnancy termination through multiple signaling pathways. GO enrichment analysis of biological processes found that misoprostol was involved in protein phosphorylation, cellular localization, proteolysis regulation, and other biological processes related to pregnancy termination. This indicates that misoprostol terminates pregnancy via multiple targets and routes. Therefore, the results of the above-mentioned studies of misoprostol are essentially consistent with the results predicted in this study regarding misoprostol's pregnancy termination targets, KEGG signal pathway enrichment analysis, and GO biological process enrichment analysis.

The mechanism of pregnancy termination is complex, involving multiple genes and signaling pathways. Misoprostol also has a variety of activities, which makes it difficult to study the mechanism of action of misoprostol in pregnancy termination. In conclusion, this study revealed the function of the target genes of misoprostol-induced pregnancy termination through network pharmacology. However, a limitation of this study is that network pharmacological analysis is purely theoretical, and the findings need to be verified by one-step experiments and clinical trials.

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## Contribution of Authors

Rui Z: Manuscript preparation and data analyse
Jing C : Study design and whole-process control
Lanlan L: data collection
Yurong Z : data collection
Wei D : data analyse
Tao Y : data analyse
Yaguang H : Study design, Corresponding author

## Conflict of interest

The authors have no conflicts of interest to declare. The authors alone are responsible for the content and writing of this article.

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