Research Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2023.53.008331

Research on the Molecular Mechanism of Combination Triptolide with Dexamethasone in Treatment of Rheumatoid Arthritis based on Bioinformatics Analysis

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ARTICLE INFO

Received: September 11, 2023

Published: September 21, 2023

Citation: Yanqin Bian, Zheng Xiang, Chengbo Zhang and Lianbo Xiao. Research on the Molecular Mechanism of Combination Triptolide with Dexamethasone in Treatment of Rheumatoid Arthritis based on Bioinformatics Analysis. Biomed J Sci & Tech Res 53(1)-2023. BJSTR. MS.ID.008331.

ABSTRACT

Objectives: Triptolide (TP), a diterpenoid triepoxide from *Tripterygium wilfordii* Hook F, can ameliorate rheumatoid arthritis (RA) through multiple molecular mechanisms. However, serious side effects limit its clinic application. Previous studies have shown that combination of TP with dexamethasone (DXM) had the synergetic effect, but the mechanism is still unknown. Therefore, this study aims to investigate the molecular mechanism of combination TP with DXM in the treatment of rheumatoid arthritis by bioinformatics analysis.

Material and Methods: The human target proteins of TP and DXM were searched in PubChem database, and the human target genes of RA were searched in Gene database from NCBI. The obtained data were imported into Ingenuity Pathway Analysis (IPA) platform to find out a potential mechanism of combination TP with DXM on RA.

Results: By searching from Gene and PubChem database, 832 target genes related with RA, 8 target proteins of TP, and 32 target proteins of DXM were found by the end of April 23rd, 2021. The main signaling pathways of combination of TP with DXM on RA was focused on cytokine signaling. Combination of TP with DXM regulated the PGE2 biosythesis through TREM-1 signaling pathway, leading to inflammation inhibtion in RA. The results also showed that DXM might reduce apoptosis of kidney cell induced by TP by JAK2/STAT signaling pathway.

Conclusion: The study indicated that combination of TP and DXM had the synergetic effect on RA by TREM-1 signaling pathway to inhibit inflammation and by JAK2/STAT signaling pathway to reduce renal toxicity.

Keywords: Triptolide; Dexamethasone; Rheumatoid Arthritis; Bioinformatics Analysis

Abbreviations: TP: Triptolide; RA: Rheumatoid Arthritis; DXM: Dexamethasone; COX: Cyclooxygenase; IPA: Ingenuity Pathway Analysis; TNF: Tumor Necrosis Factor; TLR: Toll-like Receptor; CIA: Collagen-Induced Arthritis; AA: Arachidonic Acid

Introduction

Triptolide (TP), a diterpenetriepoxide biologically active natural product, is isolated from the root of *Tripterygium wilfordii* (TW, a traditional Chinese medicine). As one of the major active ingredients of TW, TP has been proved to be effective in the treatment of a variety of inflammatory and autoimmune diseases, especially rheumatoid arthritis (RA) [1]. However, the clinical use of TP is limited because of its severe toxicities on digestive, urogenital, reproduction and blood circulatory systems [2,3]. Therefore, TP is often combined with other herbal medicines or western modern drugs with the aim to reduce side effects or toxicity, or to obtain a synergistic or additive pharma-

cological effect in clinical practice, [4,5]. Dexamethasone (DXM), an adrenocorticosteroid drug, is widely used as an anti-inflammatory and immunosuppressive drug. The accumulated evidence suggested that DXM can inhibit multiple inflammatory cytokines release like as tumor necrosis factor (TNF)–α, interleukin (IL)-1, IL-6 and so on and is often combined with TP for treating multiple myeloma, autoimmune encephalomyelitis or other diseases [6-8]. Previous animal studies in our lab found TP had good effect on inflammation and pannus formation of RA [9], but the mechanism of conbination of TP and DXM on RA was still unknown. In this study, target proteins of TP and DXM and genes of RA were collected from PubChem and Gene database. Based on the IPA analysis platform, pharmacological networks for TP and DXM were built up.

Furthermore, the functions, upstream regulators and signaling pathways of networks were analyzed to find a potential mechanism of combination of TP with DXM on RA. In addition, based on the classification of toxic functions in IPA, the toxic effect of TP on human body was explored. The study will certainly contribute to explain the effect mechanism of TP combinated DXM on RA and the toxic effect of TP on human body. The result will provide support for TP combined with DXM on RA treatment in clinical practice in further.

Materials and Methods

Searching the Target Proteins and Genes

The human target proteins of Triptolide (CID:107985) and Dexamethasone (CID:5743) were searched in PubChem platform (http://pubchem.ncbi.hlm.nih.gov), which can provide small organic molecules of biological activity data by the US National Institutes of Health (NIH) and consists of three dynamically growing primary databases: PubChem Compound, PubChem Bioassay, and PubChem Substance. The word "Triptolide" or "Dexamethasome" was searched in PubChem Compound. Given that the bio-information might be cross-referenced in other National Centers of Biotechnology Information (NCBI) database, the target proteins of active compounds which tested in bioassays could be collected in PubChem. The categories of target proteins were limited in Homo sapiens. The human target proteins of TP combined with DXM group were from TP target proteins and DXM target proteins. The human target genes related with RA were searched GENE database in NCBI site. RA were used as a key word in GENE database searching. The categories of target genes were limited in Homo sapiens. The obtained data were saved as excel form for the next step study.

Bioinformation Analysis With IPA

The human target proteins and genes data acquired in the first step were imported into IPA platform. The molecules we imputed to the IPA were termed "focus molecules". IPA generated the focus molecules into a set of networks base on different bio-functions. Molecules were represented as nodes, and the biological relationship between two nodes is represented as an edge (line). All edges are supported by at least 1 reference from the literature, from a textbook, or from canonical information stored in the IPKB. Nodes were displayed using various shapes that represent the functional class of the gene product. The networks were ranked by the scores which calculated by IPA and represented the significance of the molecules for the network. The target proteins networks can be built up for TP, DXM and RA. The major information included top biological pathway network information, biological functions, Toxicol functions, canonical pathways and other related bio-analytical information. In order to investigate the different mechanism between Trip, DXM and TP combined with DXM on RA, the canonical pathways analysis was performed under the compare module of IPA. Using Fisher's exact test, IPA determined the significance of the association between the focus molecules and the canonical pathways.

Results

The Canonical Pathways and the Biological Functions of Targets Proteins of TP and DXM

By searching from PubChem data online, 8 human targets proteins of TP and 32 human target proteins of DXM were found from PubChem database cut-off time on April 23rd, 2021. The details were shown on Tables 1 & 2. The molecular networks of TP and DXM targets proteins were shown in (Figures 1A & 1B). The top related canonical pathways of TP and DXM targets proteins were different. Based on the classification of signaling pathways in IPA, we found most signaling related with TP targets were focused on cytokine and cellular immune; most DXM targets were focused on cytokine, intracellular and second messenger signaling and nuclear receptor signaling; From the (Figure 1) CD, it was shown that top 5 biological functions of TP were related to inflammation and cell survival and top 5 biological functions of DXM were related to oxidation reaction and gene expression.

Table 1: The human target proteins of TP.

Name	GI No.
nucleotide-binding oligomerization domain-containing protein 1	5174617
sphingosine 1-phosphate receptor 3	38788193
Chain A, Human Bcl2-A1 In Complex with Bim-Bh3 Peptide	167013344
Janus kinase 2	119579178
TDP1 protein	79154014
Sphingosine-1-phosphate receptor 4	15929025
serine/threonine kinase 33	12830367
Kruppel-like factor 5	124263658

Table 2: The human target proteins of Dexamethasone.

Name	GI No.
nuclear factor erythroid 2-related factor 2 isoform 2	224028257
multidrug resistance-associated protein 1	134142337
cystic fibrosis transmembrane conductance regulator	90421313
nuclear factor erythroid 2-related factor 2 isoform 1	20149576
glucocorticoid receptor isoform gamma	66528677
Cytochrome P450 3A4	116241312
Cytochrome P450 2D6	84028191
Cytochrome P450 2C19	60416369
Cytochrome P450 2C9	6686268
Glucocorticoid receptor	121069
Cytochrome P450 1A2	117144
Carbonic anhydrase 2	115456
Monoamine oxidase type B	113980
Monoamine oxidase type A	113978
Androgen receptor	113830
Thromboxane-A synthase	254763392
Transcription factor p65	62906901
Peroxisome proliferator-activated receptor gamma	13432234
Peroxisome proliferator-activated receptor alpha	3041727
Mineralocorticoid receptor	126885
multidrug resistance protein 1	42741659
mitogen-activated protein kinase kinasekinase 3 isoform 1	42794767
Chain B, The Structure of Wild-Type Human Hadh2 Bound to Nad+ At 1.2 A	122921311
Chain A, The Structure of Wild-Type Human Hadh2 Bound to Nad+ At 1.2 A	122921310
AR protein	124375976
TDP1 protein	79154014
estrogen nuclear receptor alpha	348019627
glucocorticoid receptor	311348376
NAD+-dependent 15-hydroxyprostaglandin dehydrogenase	1203982
hypoxia-inducible factor 1, alpha subunit	32879895
peroxisome proliferator activated receptor gamma	216409692
unnamed protein product	14598960

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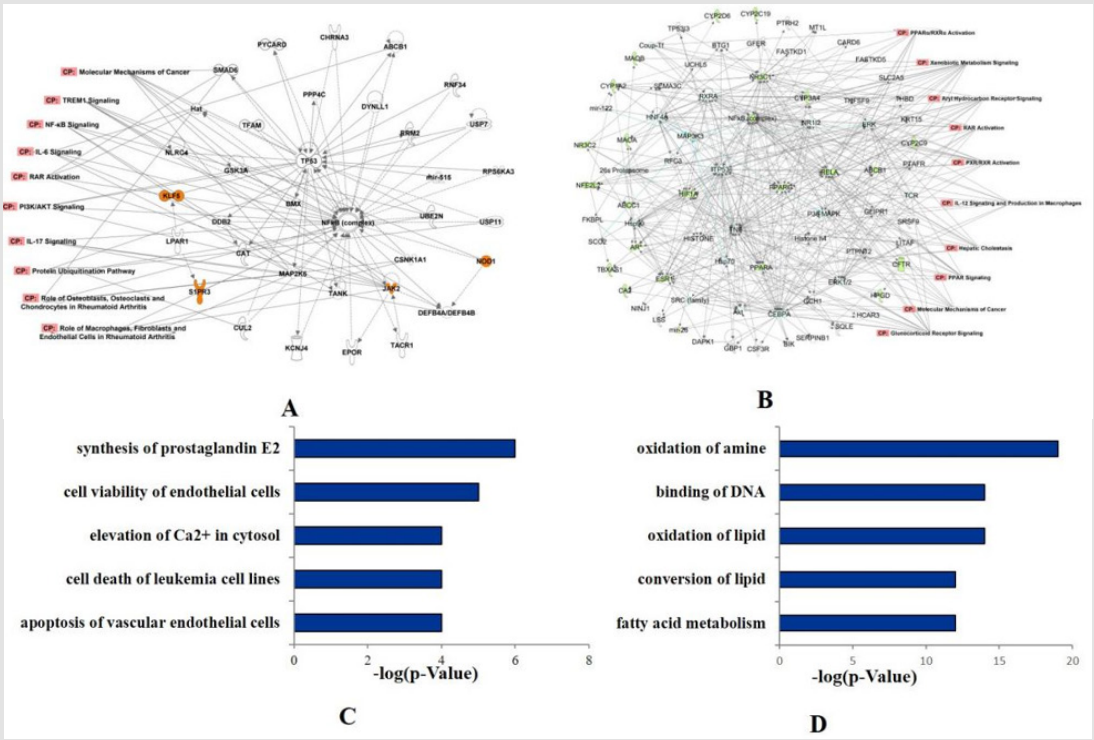

Figure 1: The molecular networks and the top 5 biological functions of TP and DXM target proteins.

Note:

A. The molecular networks of TP target proteins;

B. The molecular networks of DXM target proteins;

C. The top 5 biological functions of TP target proteins;

D. The top5 biological functions of DXM target proteins.

Regulation of TP Target Proteins to Synthesis of Prostaglandin E2 (PGE2) and DXM Target Proteins to Oxidation Reaction and Gene Expression

As shown in (Figure 1), the first biological functions of target proteins of TP and DXM respectively were to regulate PGE2 synthesis and oxidation of amine. According to the classification of diseases and functions, we knew that PGE2 was correlation with inflammation reaction more and oxidation of amine, binding of DNA and oxidation of lipid were related with energy production and gene expression. To investigate the effect of TP combination with DXM on RA, we firstly analyzed the TP and DXM target proteins successively. As shown in (Figure 2A), the synthesis of PGE2 was regulated by JAK2, KLF5 and S1PR3 and STAT3 was an important molecule for synthesis of PGE2. As red circle shown in (Figure 2B), it was well known that the target proteins of DXM regulating oxidation reaction and gene expression had a lot to do with cytochrome P450 that was a key enzyme related with drug metabolism [10].

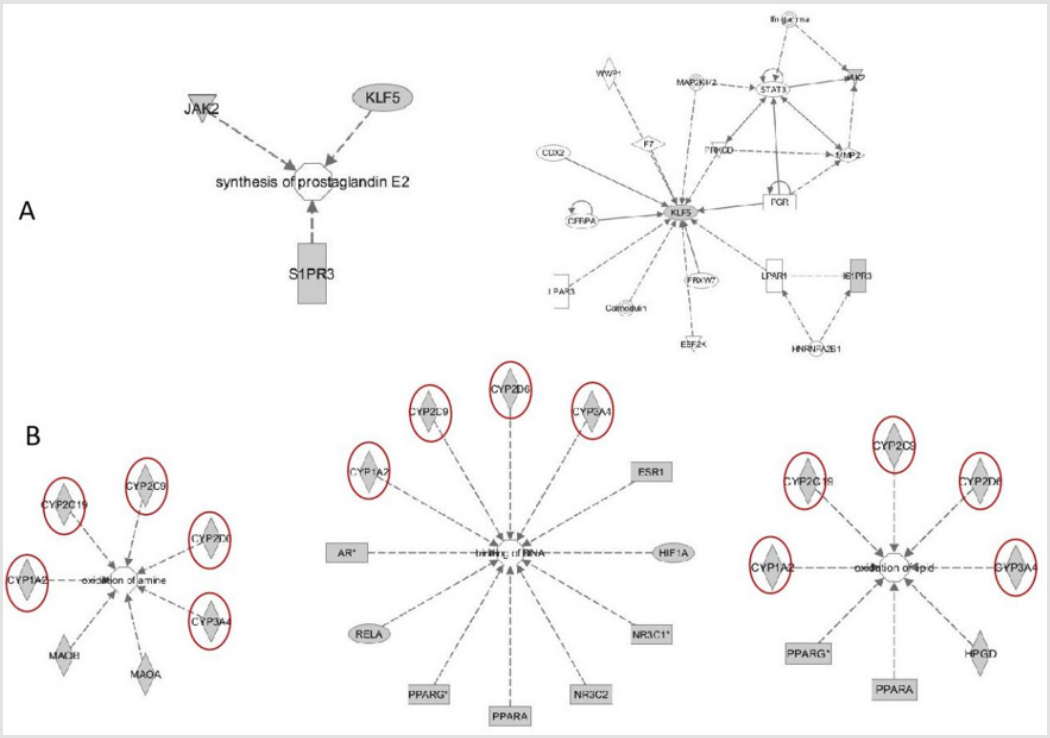

Figure 2: Target proteins of TP regulating to PGE2 synthesis and DXM regulating to oxidation reaction and gene expression.

Note:

A. Target proteins of TP regulating to PGE2 synthesis and upstream regulated network related to;

B. Targets proteins of DXM regulating to oxidation reaction and gene expression.

Combination of TP with DXM Regulated the PGE2 Biosythesis Through TREM-1 Signaling Pathway, Leading to Inflammation Inhibition in RA

From the Figures 1 & 2, we had known that most of shared signaling related with TP and DXM target proteins were focused on cytokine signaling and target proteins of TP regulated to PGE2 synthesis. Therefore, biosynthesis metabolic pathways and cytokine signaling pathways were paid close attention to. The details were shown on (Figure 3). Proteinoid biosynthesis was the only biosynthesis metabolic pathways of RA, TP+ DXM and DXM groups, not TP. The top shared cytokine signaling pathway of four groups was TREM-1 signaling.

As shown in results above, TP was not involved in the process of PGE2 biosythesis metabolic pathways but related to the signaling pathways of PGE2 effects. From the (Figure 4A), it was well known that DXM related to the biosynthesis of thromboxane A2 (TXA2). We all knew that TXA2 would transform into stable TXB2 and play the similar pro-inflammation effects to PGE2. From the (Figure 4B), the results showed TP regulated inflammation response by TREM-1/JAK2 signaling and DXM regulated it by TREM-1/NF-κB signaling. But PGE2 influenced TREM-1 expression. Studies had proved that regulation of TREM-1 and the soluble form of TREM-1 expression by PGE2 may modulate the inflammatory response [11].

DOI: 10.26717/BJSTR.2023.53.008331

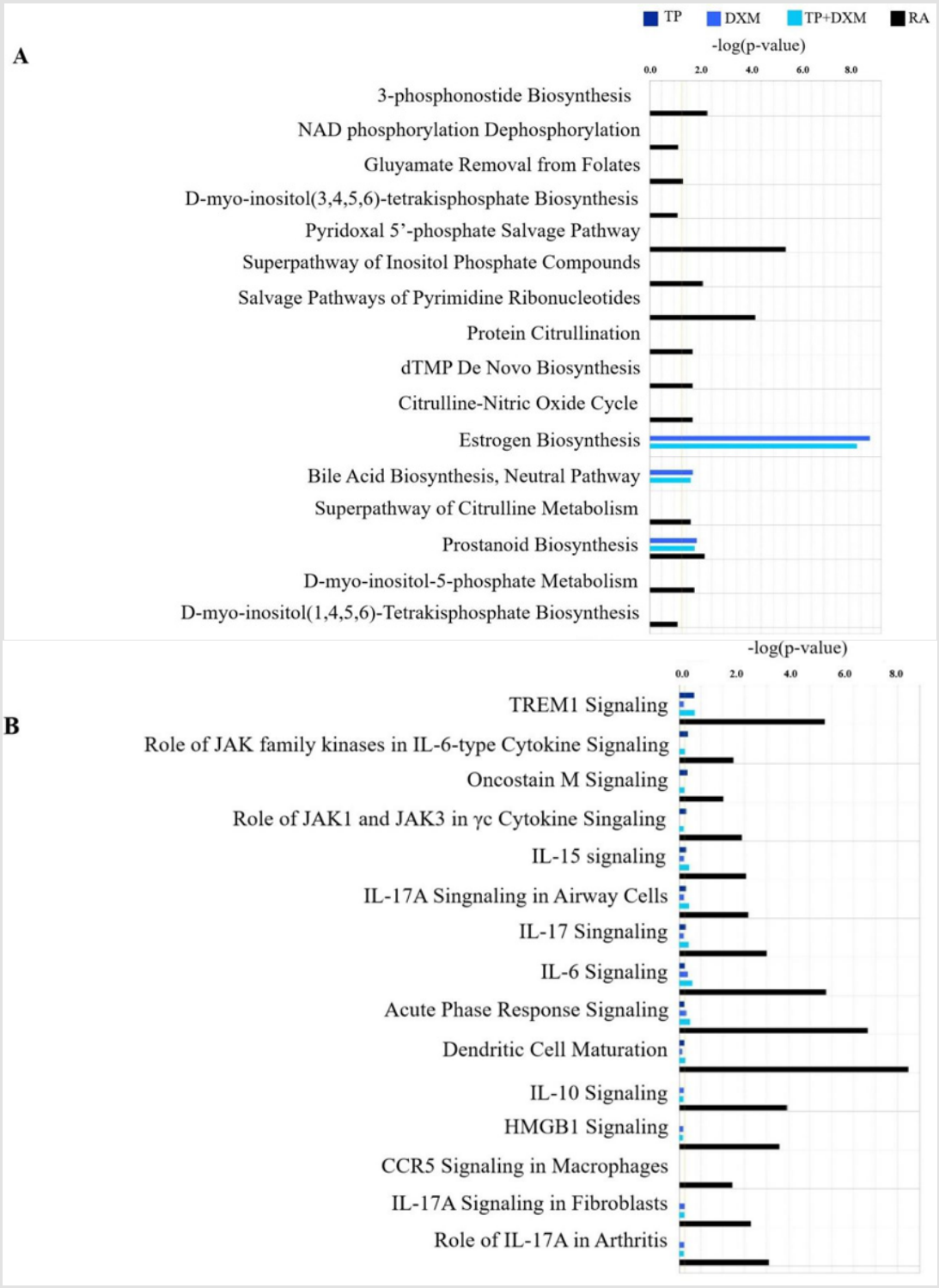

Figure 3: The canonical pathways in RA, TP+ DXM, TP and DXM groups in biosynthesis metabolic pathways and cytokine signaling pathways.

Note:

A. Biosynthesis metabolic pathways;

B. Top 15 Cytokine signaling pathways.

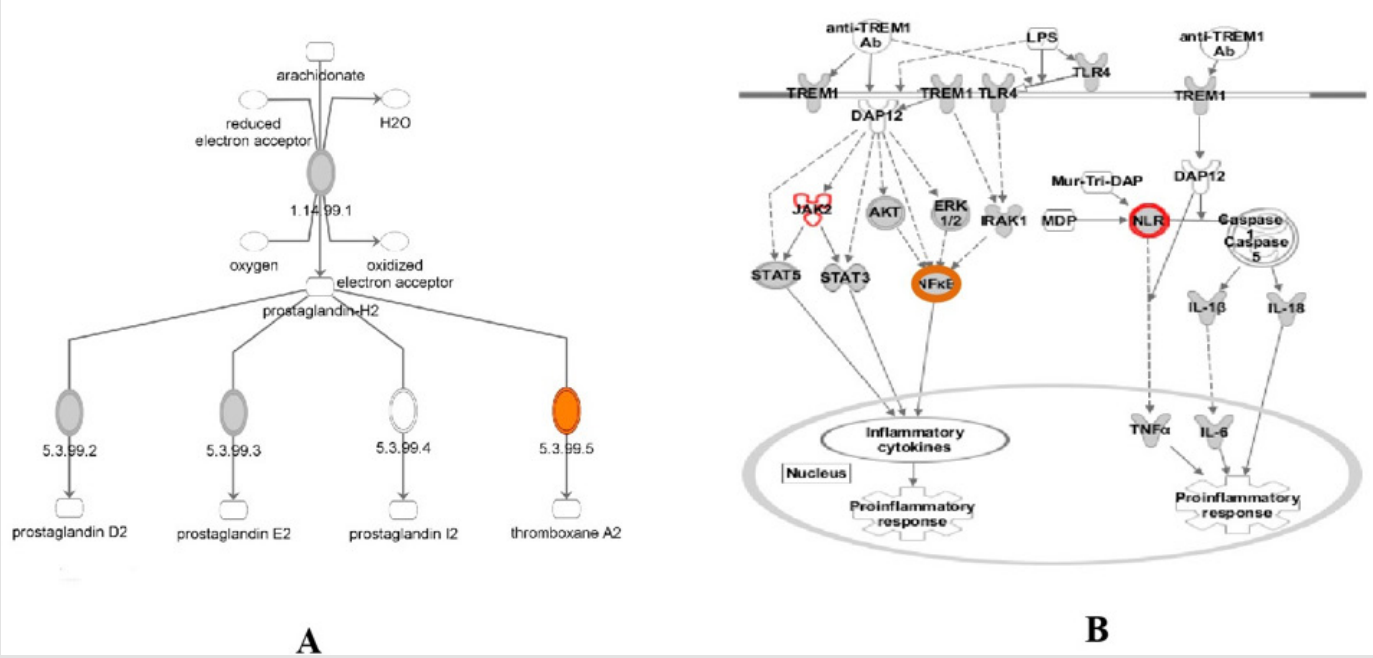

Figure 4: Prostanoid biosynthesis metabolic pathway and TREM-1 signaling pathway.

Note:

A. Prostanoid biosynthesis metabolic pathway. The grey nodes represented the RA genes, the orange nodes represented the targets proteins of TP+ DXM and DXM. There was no TP targets in this pathway.

B. TREM-1 signaling pathway. The purple circles and grey nodes represented the RA genes, the red nodes represented the target proteins of TP, the orange nodes represented the target proteins of DXM.

DXM Might Reduce Apoptosis of Kidney Cell Induced by TP by JAK2/STAT Signaling Pathway.

A growing body of evidence suggested that TP was toxic to the human body. Based on the toxic classification of diseases or functions in IPA, we found TP had significant toxic effect to kidney. As shown in (Table 3), TP is involved in the apoptosis of kidney cell lines which are related to JAK2 molecule. Although only one target protein related to apoptosis of kidney cell lines, the result was in accordance with clinical reports about TP having renal toxicity. The results showed that TP promoted apoptosis of kidney cell by JAK2/STAT signaling pathway, but DXM may interfer the effects of TP on kidney cell shown in (Figure 5). Although the mechanism of DXM involved in the apoptosis of kidney cell was unclear in this study, it was true that the effects of TP and DXM were correlation with kidney, which was consistent with clinical reports.

Table 3: The molecule and functions involved in side effect of TP to human body.

Categories	Diseases or Functions Annotation	p-Value	Molecules
Renal Necrosis /Cell Death	apoptosis of kidney cell lines	8.15E-02	JAK2

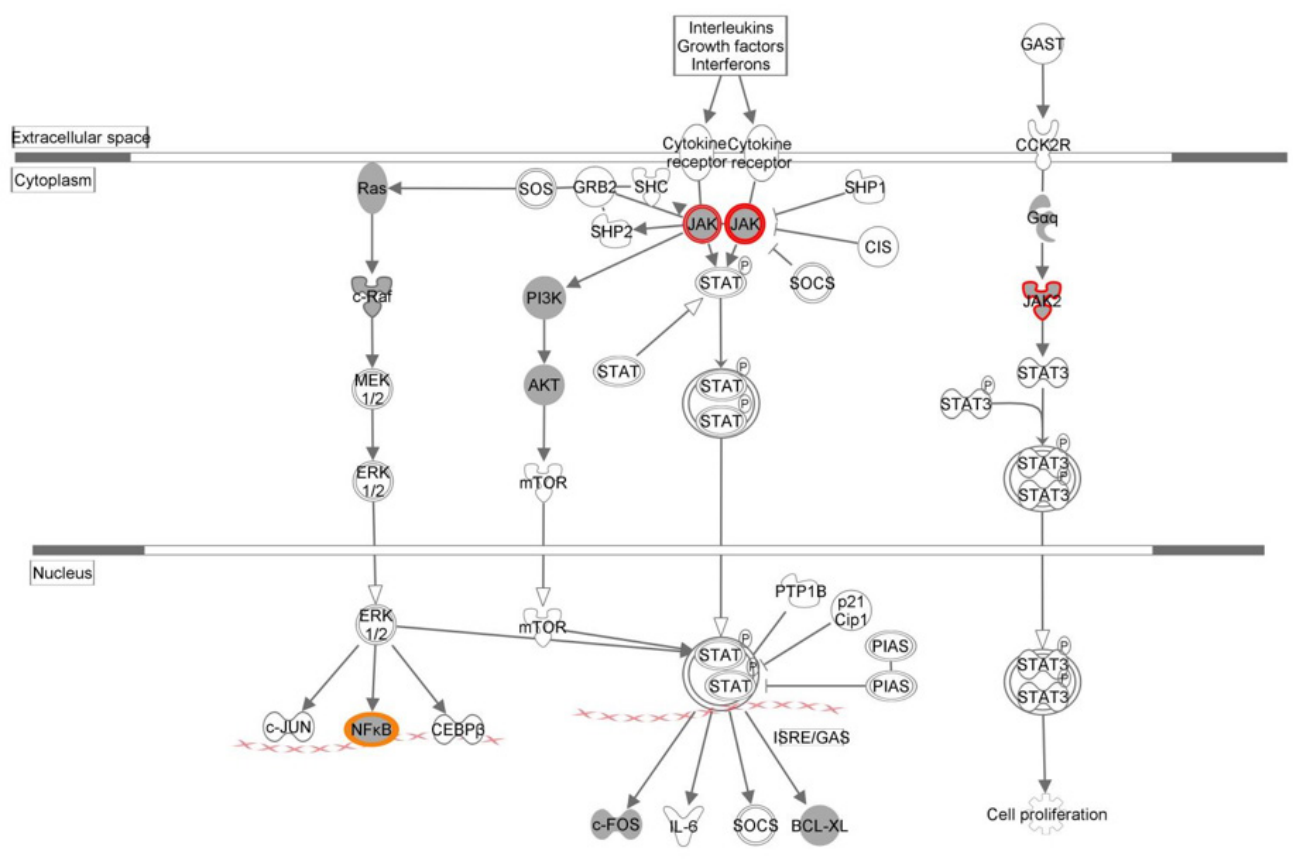

Figure 5: The JAK/STAT signaling pathway.

Note: The grey nodes represented molecules of involving apoptosis of kidney cell; the red circles represented the target proteins of TP; the orange circle represented the targets proteins of DXM.

Discussion

In this study, we obtained target proteins and genes from PubChem and GENE database and analyzed the interrelation between them using IPA soft platform. The results demonstrated that TP combined with DXM may reduce arachidonic acid (AA) metabolite PGE2 and TXA2 synthesis and inhibit inflammatory response related to RA by TREM-1 signaling pathway. PGE2 and TXA2, both members of eicosanoids derivatives, were involved in inflammatory responses [12]. But they depended on the two distict enzymes with cyclooxygenase (COX) activity, COX-1 and COX-2, respectively [13]. PGE2 was synthesized from AA through the COX-2 pathway and was generally recognized as a potent lipid regulator of active inflammation [14], while TXA2 was converted from AA by COX-1 that was the only isoform available in platelets and promoted platelet aggregation and vasoconstriction [15,16]. Our results showed the main biological functions of TP was regulation the synthesis of PGE2 and DXM was modulation the synthesis of TXA2. However, TP regulated the synthesis of PGE2 not by involving in PGE2 metabolic pathway but by influencing PGE2 related to signaling pathway. TREM-1 is a immunoglobulin-like cell surface receptor mainly expressed on neutrophils and a subset of CD14+ monocytes [17]. TREM-1 expression is increased by various Toll-like receptor (TLR) ligands during acute inflammation [18,19]. Moreover, a soluble form of TREM-1 was released into the blood of human patients with sepsis as well as multiple other inflammatory disorders, including pneumonia, acute pancreatitis and peptic ulcer disease [20-23].

TREM-1 was expressed on CD14+ cells in rheumatoid synovial tissue and synovial macrophages from mice with collagen-induced arthritis (CIA). The blockade of TREM-1 ameliorated CIA without affecting T cell and B cell immune responses to the inducing antigen [24]. In RA patients, the presence of high levels of functionally active TREM-1 in RA synovium may contribute to the development or maintenance of RA, or both [25]. In resident murine peritoneal macrophages stimulated by LPS, up-regulation of TREM-1 expression was specific to PGE2, especially in late phase (>2 h after stimulation) [11]. But human monocyte/macrophages did not depend on PGE2 for up-regulation of TREM-1 [24]. TREM-1, as an inflammation amplifier, induced multiple pro-inflammatory cytokines release [18,26].

Therefore, it was very hopeful to become a new therapeutic target for RA. In this study, TP, DXM and TP combined with DXM all involved in TREM-1 signaling pathway as shown in (Figure 4B), although they were not acting on TREM-1 directly. A study found TP inhibited the expression of COX-2 and the secretion of PGE2 in synovial fibroblasts from RA [27]. These suggested that TP combined with DXM may inhibit inflammation by TREM-1 triggering to alleviate RA. In this study, we also found TP promoted apoptosis of kidney cell by JAK2/STAT signaling pathway, but DXM may interfere with the effects of TP on kidney cell. According to clinical reports, the main toxic effects of TP were focused on digestive, urogenital, reproduction and blood circulatory systems, but our results only showed renal toxicity.

This may be the reason that only 4 target proteins of TP were analyzed, JAK2, KLF5, S1PR3 and NOD1. There studies reported that TP induced liver injury was related inhibition of mitochondrial respiratory chain, which inducing the secondary β-oxidation impairment, micro vesicular steatosis, hyper lactacidemia and enhanced oxidant stress [28]. And The liver and the kidney toxicity of TP on rat pretreated with DXM were significantly reduced by P4503A induced the metabolism acceleration of TP [29]. In accord with reports, our results displayed target proteins of DXM regulating to oxidation reaction and gene expression had a lot to do with CYP450 as shown in the (Figure 3). Our results suggested that TP combined to DXM on RA treatment may reduce toxicity of TP treatment RA alone. But the results have needed more experiments to confirm.

Acknowledgements

This work was funded by the National Natural Science Funds of China (82004166), Shanghai Municipal Science and Technology Commission (22ZR1453100, 21Y11921500), Training Program for High-caliber Talents of Clinical Research at Affiliated Hospital of SHUTCM (2023LCRC24).

Authors' Contributions

YB was accountable for the gathering, assembling, and composition of the primary manuscript. ZX was involved in the composition of the primary manuscript. CZ contributed to the creation of illustrations. LX were liable for the manuscript review. All authors evaluated and approved the last version.

Declarations

Ethics Approval and Consent to Participate

Non applicable

Constant For Publication

All authors agreed to the publication of this manuscript.

Competing Interests

The authors declare that they have no competing interests.

Availability of Data and Materials

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2023.53.008331

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