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Study on the Mechanism of the Buqi Tongqiao Formula in Regulating the PI3K/AKT/mTOR Pathway to Intervene in IgA Nephropathy in Rats

Jinjiang Xu [1, 2], Man Zhang [2], Qiuye Wu [1, 2], Xiongbin Gui [2], Hang Xu [3, *]

[1] Guangxi University of Chinese Medicine, Nanning, Guangxi, CO 530001, China
[2] The First Affiliated Hospital of Guangxi University of Chinese Medicine, Nanning, Guangxi, CO 530020, China
[3] Guangxi Traditional Chinese Medicine School, Nanning, Guangxi, CO 530023, China

*** Corresponding author:** Hang Xu (Email: 245090908@qq.com)

Abstract: Objective: To explore the molecular mechanism by which Buqi Tongqiao Formula (BQTQF) improves renal injury in rats with IgA nephropathy (IgAN) by regulating the PI3K/AKT/mTOR pathway. **Methods:** The IgAN rat model was established by intragastric administration of BSA, intraperitoneal injection of CCl_4, and combined intravenous injection of LPS. Thirty rats were randomly divided into the blank group, model group, and BQTQF group. After successful model establishment, the rats were administered continuously for 8 weeks, once a day. Renal function was evaluated by determining 24-hour urinary protein, Scr, and BUN levels. Pathological damage of renal tissue in IgAN rats was observed by HE staining. RT-qPCR and Western blot were used to detect the mRNA and protein expression levels of PI3K, AKT, and mTOR in renal tissue of IgAN rats. **Results:** Compared with the blank group, the levels of 24hUTP, Scr, and BUN in the model group were significantly increased ($P<0.01$), renal pathological damage was aggravated, and the mRNA transcription levels and protein expression of PI3K, AKT, and mTOR in renal tissue were elevated. After intervention with BQTQF, the renal function of IgAN rats was significantly improved, histopathological damage was alleviated, and the mRNA transcription levels and phosphorylated protein expression of PI3K, AKT, and mTOR were reduced. Conclusion: BQTQF alleviates renal pathological damage and improves renal function in IgAN rats by regulating the PI3K/AKT/mTOR signaling pathway.

Keywords: IgA Nephropathy; Buqi Tongqiao Formula; PI3K/AKT/mTOR; Renal Injury.

1. Introduction

IgA nephropathy (IgAN)) ranks among the most prevalent primary glomerulonephritis globally. It is defined by the accumulation of IgA immune complexes within the glomerular mesangium, which frequently progresses to chronic kidney impairment and can advance to end-stage renal failure.[1]. Despite increasing understanding of IgAN in recent years, its exact pathogenesis remains unclear, and current treatment strategies have limitations and cannot effectively halt disease progression[2,3]. Overactivation of the PI3K/AKT/mTOR pathway promotes mesangial cell proliferation and extracellular matrix accumulation[4], exacerbating glomerulosclerosis. Additionally, this pathway exacerbates renal inflammation and damage by regulating the production of proinflammatory cytokines and chemokines. Therefore, regulating the PI3K/AKT/mTOR pathway may provide new strategies for the treatment of IgAN[5,6] .

Traditional Chinese medicine (TCM) has rich experience and unique advantages in the treatment of kidney diseases[7]. Buqi Tongqiao Formula (BQTQF) is an empirical traditional Chinese medicine compound of Professor Gui Xiong-bin, The compound comprises three key ingredients: Astragalus membranaceus (Fisch.) Bge., Codonopsis pilosula (Franch.) Nannf., and Glycyrrhiza uralensis Fisch, *Xanthium sibiricum* Patr., *Magnolia biondii* Pamp., *Asarum sieboldii* Miq., *Schizonepeta tenuifolia* (Benth.) Briq., *Platycodon grandiflorus* (Jacq.) A.DC., *Otolithum*, *Cimicifuga foetida* L., and *Bupleurum chinense* DC. It has the effects of replenishing qi and consolidating the exterior, strengthening healthy qi and eliminating pathogenic factors, and has shown potential therapeutic effects on IgAN in clinical practice; however, its specific mechanism of action remains unclear[8,9]. In this study, we will construct a rat model of IgA nephropathy to evaluate the improvement effect of BQTQF on renal pathological injury and further explore its regulatory mechanism on PI3K/AKT/mTOR pathway, aiming to reveal the molecular mechanism of BQTQF and provide new theoretical basis and practical guidance for clinical application.

2. Materials

2.1. Major Instruments

The main instruments used in this study include the YJX20/1 Circulating Decoction and Packaging Combination Machine (Beijing Donghuayuan Medical Equipment Co., Ltd.), the BS-240VET fully automatic biochemical analyser (Mindray Medical International Limited), the BX63 upright fluorescence microscope (Olympus Corporation, Japan), the ASP300S fully automatic tissue dehydrator (Leica Microsystems GmbH, Germany), the Histostar tissue embedding machine, HM355S Pathology Microtome (Thermo Fisher Scientific, USA), and the DP360 Fully Automatic Staining and Mounting Machine (Dakowe Biotechnology Co., Ltd.), among others.

2.2. Major Medicines and Reagents

Bupleurum chinense DC, *Codonopsis pilosula* (Franch.) Nannf., *Astragalus membranaceus* (Fisch.) Bge., *Schizonepeta tenuifolia* (Benth.) Briq., *Platycodon grandiflorus* (Jacq.) A. DC., *Magnolia biondii* Pamp., *Cimicifuga foetid*a L. herbal slices were all sourced from

Guangxi Xianju Traditional Chinese Medicine Technology Co., Ltd. (batch numbers: 20240103, 20240103, 20240601, 20240201, 20240201, 20231101, 20240304); *Glycyrrhiza uralensis* Fisch, *Xanthium sibiricum* Patr. herbal slices were sourced from Guangxi Wanbaotang Pharmaceutical Co., Ltd. (batch numbers: 240304601,240300805); *Asarum sieboldii* Miq. herbal slices were sourced from Sichuan Xinhuahuo Traditional Chinese Medicine Herbal Slices Co., Ltd. (batch number: 2403101); Otolithum herbal slices were sourced from Sichuan Hongkangyuan Co., Ltd. (batch number 240301). Benazepril Hydrochloride Tablets (Batch No. H20233426; specification: 10 mg/tablet) were purchased from Zhejiang Huahai Pharmaceutical Co., Ltd.

BSA, LPS (Sigma-Aldrich, USA, batch numbers V900933 and L2880); CCL4, castor oil (Sinopharm Chemical Reagents Co., Ltd., batch numbers C805332 and 69006811); Scr and BUN detection kits (Mindray Medical International Limited, batch numbers 10500045700 and 10500045200); HE staining kit (Beijing Solarbio Science & Technology Co., Ltd., number G1120); PI3K, p-AKT, AKT, mTOR, p-mTOR, β-actin rabbit polyclonal antibodies (Wuhan Sanying, 20584-1-AP, 10176-2-AP, 66444-1-Ig, 81670-1-RR, 67778-1-Ig, 66009-1-Ig); Phospho-PI3K rabbit polyclonal antibody (Thermo Fisher, PA5-17387), HRP goat anti-rabbit (Wuhan Sanying, SA00001-2).

2.3. Animals

30 male SD rats (180-200 g) were bought from Hunan Slaike Jingda Laboratory Animal Co., Ltd. (License SCXK (Xiang) 2019-0001) and kept in an SPF barrier environment with 50%-60% humidity, 25°C temperature, and 12h light-dark cycle. They had free access to food and water. The study got the Experimental Animal Ethics Committee of Guangxi University of Traditional Chinese Medicine's approval (DW20240319-060).

3. Method

3.1. Drug Preparation

BQTQF: *Astragalus membranaceus* (Fisch.) Bge. 20 g,*Codonopsis pilosula* (Franch.) Nannf. and *Glycyrrhiza uralensis* Fisch. 12 g each,*Xanthium sibiricum* Patr. 6 g,*Magnolia biondii* Pamp. 10 g,*Asarum sieboldii* Miq. 2 g,*Schizonepeta tenuifolia* (Benth.) Briq. 15 g,*Platycodon grandiflorus* (Jacq.) A. DC. Otolithum 10 g each,*Cimicifuga foetida* L. 3 g,*Bupleurum chinense* DC. 9 g. Take the above herbal slices, mix them evenly, add 1,500 mL of distilled water. The mixture was soaked for 30 minutes, brought to a boil over high heat, and then simmered gently for 60 minutes. After filtration, the residue was refluxed with an additional 1,500 mL of distilled water, followed by simmering and filtration. The two resulting decoctions were combined, filtered, and cooled. The combined filtrate was concentrated under reduced pressure at approximately 50°C using a rotary evaporator to a final concentration of 3 g/mL (based on raw herb weight), and stored at -20°C for future use.

3.2. IgA Nephropathy Model and Grouped Drug Administration

Healthy SD rats were adaptively fed for 1 week and then randomly divided into a control group (10 rats, Normal) and a model group (20 rats, Model). The model group rats were modified according to the method of Lu Huiyu [10]et al. to establish an IgAN rat model. The specific procedures were as follows: (1) BSA crystalline powder was mixed with distilled water for dilution, and administered orally at a dose of 400 mg/kg every other day for 8 weeks; (2) CCl_4 plus castor oil were mixed in a 1:3 volume ratio and administered via subcutaneous injection once weekly for 9 weeks; (3) 0.05 mg LPS (prepared in PBS buffer) was administered via tail vein injection at weeks 6 and 8.

After the model was successfully established, the rats were randomly divided into the following groups: the model group (Model) and the BQTQF group, with 10 rats in each group. (1) Normal and Model groups: were given equal volumes of physiological saline by gavage; (2) BQTQF: this study used a clinically equivalent dose of 9.81 g/kg for the BQTQF. Administered by gavage once a day for 28 consecutive days.

3.3. Sample Collection

At the end of the 8th week of drug intervention, rats were allowed to eat but not drink water. Urine samples were collected from all groups of rats over a 24-hour period. Rats were anaesthetised with 0.3 mg/100 g of 2% pentobarbital sodium administered intraperitoneally, and blood samples were collected via the abdominal aorta. After blood collection, the rats were quickly euthanised, and both kidneys were removed. The left kidney was cut in half and fixed in 4% paraformaldehyde for fixation.

3.4. 24 Hour Urine Total Protein Measurements

Twenty-four-hour urine samples collected as described in section 2.3 were used to determine the 24-hour urine total protein (24h UTP) content using a urine protein assay kit (colorimetric method).

3.5. Serum Scr and BUN Measurements

Blood samples were allowed to stand at room temperature for 2 hours, then centrifuged at 3500 rpm at 4°C for 15 minutes. The upper serum layer was separated and assayed for Scr and BUN levels using a fully automatic biochemical analyser.

3.6. Hematoxylin-Eosin (HE) Staining

Kidney tissues were fixed by immersion in 4% paraformaldehyde for 48 hours. After fixation, the tissues were sequentially dehydrated, cleared, embedded in paraffin, and sectioned into 5 μm thick consecutive sections. The sections were spread on a slide in 45°C warm water for 1~2 minutes, then removed with adhesive slides once fully unfolded. The sections were then baked at 98°C for 20 minutes and stored for later use. The sections were routinely dewaxed to water, stained with hematoxylin and 1% eosin solution, and mounted with neutral balsam. Renal tissue morphological changes were observed under a light microscope, photographed, and stored.

3.7. RT-qPCR

One hundred milligrams of renal tissue from each group were weighed and added to Trizol solution, homogenised, and then incubated on ice for 30 min. Total RNA was extracted using a column-based extraction method. The 230/260 and 260/280 ratios were measured using a ultraviolet (UV) spectrophotometer. Complementary DNA (cDNA) was synthesised according to the manufacturer's instructions for the reverse transcription kit (reaction conditions: 37°C for 2 min, 50°C for 15 min, 85°C for 2 min; reaction volume: 20

μL). For quantitative real-time PCR (qPCR), reactions were performed using cDNA as the template (reaction program: 95°C pre-denaturation for 10 min, followed by 40 cycles of 95°C denaturation for 10 sec and 60°C annealing/extension for 10 sec; reaction volume: 20 μL). Each group had 3 independent replicates. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) served as the housekeeping gene for normalization. Relative expression levels of target genes were determined via the $2^{(-\Delta\Delta Ct)}$ method, with primer sequences provided in Table 1.

Table 1. Primer sequence design table

Gene name	Forward primer (5'-3')	Reverse primer (5'-3')
PI3K	CACCTCCGCAACCAATCCTGAC	AGCTCGAACTCTGTCTCCTTCTGG
AKT	TCACCTCTGAGACCGACACC	CGACGTAGCCATTGTGAAGGAG
mTOR	CTGTCTGATTCTTACCACGC	CGGTTCATACCCTTCTCTTT
β-actin	GGCTGTATTCCCCTCCATCG	CCAGTTGGTAACAATGCCATGT

3.8. Western Blot

One hundred milligrams of renal tissue from each group were weighed, and 1 mL of RIPA lysis buffer was added to lyse the tissue. Total protein was extracted, and its concentration was determined using the BCA method. Protein samples were mixed with SDS loading buffer and subjected to SDS-PAGE electrophoresis (concentrating gel: 80 V for 30 min; separating gel: 180 V for 60 min). Proteins were then transferred to a PVDF membrane (200 mA for 60 min), blocked with 5% non-fat dry milk on a shaker at room temperature, incubated with primary antibodies at 4°C overnight, and then with secondary antibodies at room temperature for 1 h. The membrane was washed three times with TBST, developed using ECL chemiluminescence, and gray values were analysed using ImageJ software.

3.9. Statistical Methods

Statistical analysis was conducted with SPSS 26.0. Data are presented as mean ± standard deviation ($\bar{X} \pm S$). For data meeting assumptions of normality and homogeneity of variances, one-way analysis of variance (ANOVA) was used for multi-group comparisons, followed by the least significant difference t-test (LSD-t) for pairwise comparisons. The Kruskal–Wallis test was employed for data that violated these assumptions. A P-value less than 0.05 was considered statistically significant.

4. Results

4.1. The Effect of BQTQF on 24-hour Urine Protein Content in IgAN Rats

Compared for the Normal group, 24-hour UTP content was significantly elevated in the Model group ($P < 0.05$), indicating successful IgA nephropathy model induction. Relative to the Model group, 8-week BQTQF intervention significantly reduced 24-hour UTP content ($P < 0.05$) (Table 2).

4.2. The Effects of BQTQF on Serum Scr and BUN Levels in IgAN Rats

Table 2. Effects of BQTQF on 24h UTP , Scr and BUN in IgAN rats ($\bar{X}$±s, n=6)

Group	24h UTP(U/L)	Scr(μmol/L)	BUN(mmol/L)
Normal	114.28±17.59	65.83±10.65	8.15±1.88
Model	522.95±49.62*	99.67±18.27*	11.45±1.43*
BQTQF	330.96±40.95▲	77.50±8.60▲	8.89±1.23▲

Note: Compared to the normal group *P<0.05, compared to the model group ▲P<0.05.

Serum Scr and BUN levels were significantly higher in the Model group than in the Normal group ($P < 0.05$), indicating successful IgA nephropathy model induction. Relative to the Model group, 8-week BQTQF intervention significantly lowered 24-hour UTP levels ($P < 0.05$, Table 2).

4.3. The Effect of BQTQF on Histopathological Damage in IgAN Rats

HE staining revealed that, compared to the normal group, rats in the model group exhibited mesangial expansion, increased mesangial matrix, vacuolation of renal tubular epithelial cells, and increased inflammatory cell infiltration in the renal interstitium, along with IgA deposition. In contrast, rats in the BQTQF group showed significant improvement in these pathological changes, including reduced mesangial expansion, decreased tubular epithelial vacuolation, diminished inflammatory cell infiltration, and attenuated IgA deposition (Figure 1).

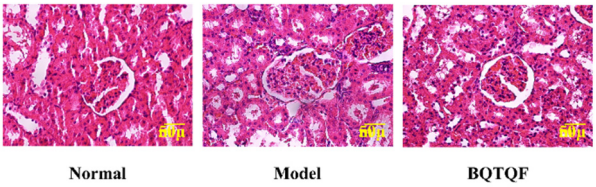

Figure 1. Effects of BQTQF on the histopathological damage of kidney tissues in IgAN rats.

4.4. Effects of BQTQF on the mRNA Expression of PI3K, AKT and mTOR in the Kidneys of IgAN Rats

RT - qPCR assay demonstrated that, compared to the normal group, the mRNA levels of PI3K, Akt and mTOR in kidney tissues of the model group were significantly increased ($P<0.05$). After administration of the BQTQF to rats in the BQTQF group, the mRNA levels of these molecules in their kidney tissues were significantly downregulated compared to the model group ($P<0.05$) (Table 3).

Table 3. Effects of BQTQF on the mRNA expression of PI3K, AKT, and mTOR in the kidneys of IgAN rats ($\bar{X}$±s, n=3)

Group	PI3K	AKT	mTOR
Normal	1.13±0.19	1.02±0.20	1.27±0.25
Model	1.88±0.12*	2.91±0.15*	3.67±0.31*
BQTQF	1.52±0.33▲	1.81±0.12▲	2.69±0.21▲

Note: Compared to the normal group *P<0.05, compared to the model group ▲P<0.05.

4.5. Effects of BQTQF on the Protein Expression of PI3K, AKT and mTOR in the Kidney Tissue of IgAN Rats.

Western blot analysis revealed that, compared to the Normal group, the protein expression levels of PI3K, Akt, and mTOR in the kidney tissue of IgAN rats were significantly upregulated (P<0.05). In contrast, these protein expression levels were markedly downregulated in the BQTQF group compared to the Model group (P<0.05) (Table 4, Figure 2).

Table 4. Effects of BQTQF on the protein expression of PI3K, AKT, and mTOR in the kidneys of IgAN rats ($\bar{X}$±s, n=3)

Group	p-PI3K/PI3K	p-AKT/AKT	p-mTOR/mTOR
Normal	0.42±0.17	0.42±0.10	0.26±0.11
Model	2.13±0.20*	1.64±0.39*	1.65±0.38*
BQTQF	1.61±0.26▲	1.01±0.24▲	0.80±0.26▲

Note: Compared to the normal group *P<0.05, compared to the model group ▲P<0.05.

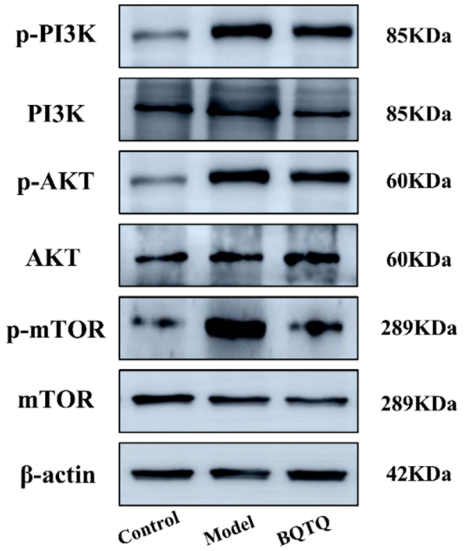

Figure 2. Effects of BQTQF on the protein expression of PI3K, AKT, and mTOR in the kidney tissue of IgAN rats

5. Conclusion

In TCM, IgAN is linked to external pathogenic factors like wind, dampness-heat, and blood stasis, as well as internal factors such as organ dysfunction and qi/blood/yin/yang deficiency [11]. It's characterized by a syndrome of root deficiency and branch excess, with intermingled deficiency and excess, where the primary deficiency involves the lungs, spleen, and kidneys, and the excess is due to wind-heat, phlegm-heat, or damp-heat [12]. The BQTQF formula focuses on tonifying lung and spleen qi to strengthen healthy qi (zhengqi) and dispel pathogenic factors and dispel external pathogens such as wind-cold-dampness toxins. Its components like Astragalus and Codonopsis tonify the spleen and boost qi, while Asarum guides the herbs to the kidneys. Schizonepeta, Platycodon, and Fishbrain stone clear heat and toxins, and resolve stagnation. Cimicifuga and Bupleurum enhance yang and lift sinking qi, and Xanthium and Magnolia flower dispel wind-dampness and unblock the meridians. Licorice harmonizes the formula [13]. This study used a rat IgAN model induced by BSA (gavage), CCl_4 (intraperitoneal injection), and LPS (intravenous injection). After 8 weeks of treatment with BQTQF, the significant reduction in 24h UTP, Scr, and BUN confirmed the formula's effectiveness in improving kidney function.

The abnormal activation of the PI3K/AKT/mTOR pathway plays a significant in the pathophysiology of IgAN [14,15]. PI3K catalyzes the phosphorylation of phosphatidylinositol to generate the second messenger PIP3, thereby activating AKT[16,17]. Activated AKT further phosphorylates mTOR, promoting cell cycle progression and cell proliferation. Moreover, activated mTOR regulates protein synthesis and cell metabolism, driving inflammatory responses and fibrosis [18]. In IgAN, the overactivation of this pathway leads to mesangial cell proliferation, extracellular matrix accumulation, and inflammatory cell infiltration, exacerbating kidney damage [19]. Histopathological findings in IgAN include widened glomerular mesangial areas, increased mesangial matrix, vacuolar degeneration of renal tubular epithelial cells, and significant inflammatory cell infiltration in the renal interstitium, along with IgA deposition. However, intervention with the BQTQF alleviated renal tissue damage in IgAN rats, indicating its renoprotective effects. It is suggested that the BQTQF may downregulate the transcription of PI3K, AKT, and mTOR mRNA and reduce the expression of PI3K, AKT, mTOR and their phosphorylated proteins, thus inhibiting the activity of the PI3K/AKT/mTOR pathway.

The results of this study indicate that the BQTQF effectively alleviates renal pathological damage and improves renal function in IgAN rats by modulating the PI3K/AKT/mTOR signaling pathway and reducing the transcription and protein expression of related factors. However, this mechanism has not yet been further verified in vitro experiments. In the future, it is planned to establish cell culture models and compare and analyze the key targets of BQTQF intervention in IgAN in depth by using inhibitors and activators of key nodes in the PI3K/AKT/mTOR pathway.

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