

ARTICLE

Analysis of mechanism of Chailing decoction preventing bladder neck contracture after transurethral resection of prostate

Haizhu FU,¹ Zhiqiang WANG,^{*,2} Jinhong QIN,³ Yanfang REN,⁴ and Wei LI¹

¹ Department of Urology, Shouguang Hospital of Traditional Chinese Medicine, Shouguang, 262700, China

² Department of Urology, Shouguang Hospital of Traditional Chinese Medicine, Shouguang, 262700, China,

³ Department of Obstetrics and Gynecology, Shouguang Hospital of Traditional Chinese Medicine, Shouguang, 262700, China

⁴ Operation Room, Shouguang Hospital of Traditional Chinese Medicine, Shouguang, 262700, China

*Corresponding author. Email: TCMwangzhiqiang@163.com, <https://orcid.org/0000-0003-1459-6602>

(Received 15 July 2022; revised 17 August 2022; accepted 25 September 2022; first published online 30 September 2022)

Abstract

Over the last few decades, numerous surgical procedures have been proposed to treat lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH). However, all are characterized by a certain rate of treatment failure due to bladder neck contracture (BNC). Treatment of secondary BNC appears to be challenging. Triamcinolone acetonide can be used to prevent BNC, but it is not ideal in improving patients' LUTS. Chailing Decoction was found to have glucocorticoid-like effect, which can prevent the occurrence of BNC and improve the LUST of patients. This study reveals the active ingredients and potential molecular mechanism of Chailing Decoction in the treatment of BNC, and provides a reference for subsequent basic research.

Keywords: lung adenocarcinoma;Ze-Qi Decoction;network pharmacology; molecular docking;RELA

Bladder neck contracture (BNC) following transurethral resection of the prostate (TURP) is a rare but feared complication with a reported incidence of 2.7–10.0%[1]. BNC typically presents with lower urinary tract symptoms and usually develops within 60 days after transurethral resection. The average time to diagnose BNC after operation was 18.5 months; However, half of the patients developed BNC within 6 months. If there is no obvious improvement in dysuria after urethral dilation, a necessary cystoscopy can confirm the diagnosis due to the possibility of BNC[2]. So far, the exact mechanism of BNC after TURP is not well understood. Many risk factors, including small prostate volume, higher International Prostate Symptom Score storage scores, preoperative uncontrolled infection,

extensive resection of the bladder neck, excessive fulguration at the bladder neck, or a large resecting loop that generates excessive heat to produce a hypertrophic scar in a small intraurethral adenoma[3]. Treatment options for BNC remain controversial; urethral dilation 18F followed by a 3-month period of intermittent self-catheterization, cold knife incision, and transurethral resection have been proposed with varying success rates. Regular long-term urethral dilation contributes to a false urethral pathway, hemorrhage, infection, and poor quality of life. About 90% of patients may need to repeat urethral dilation within the first 2 years[4].

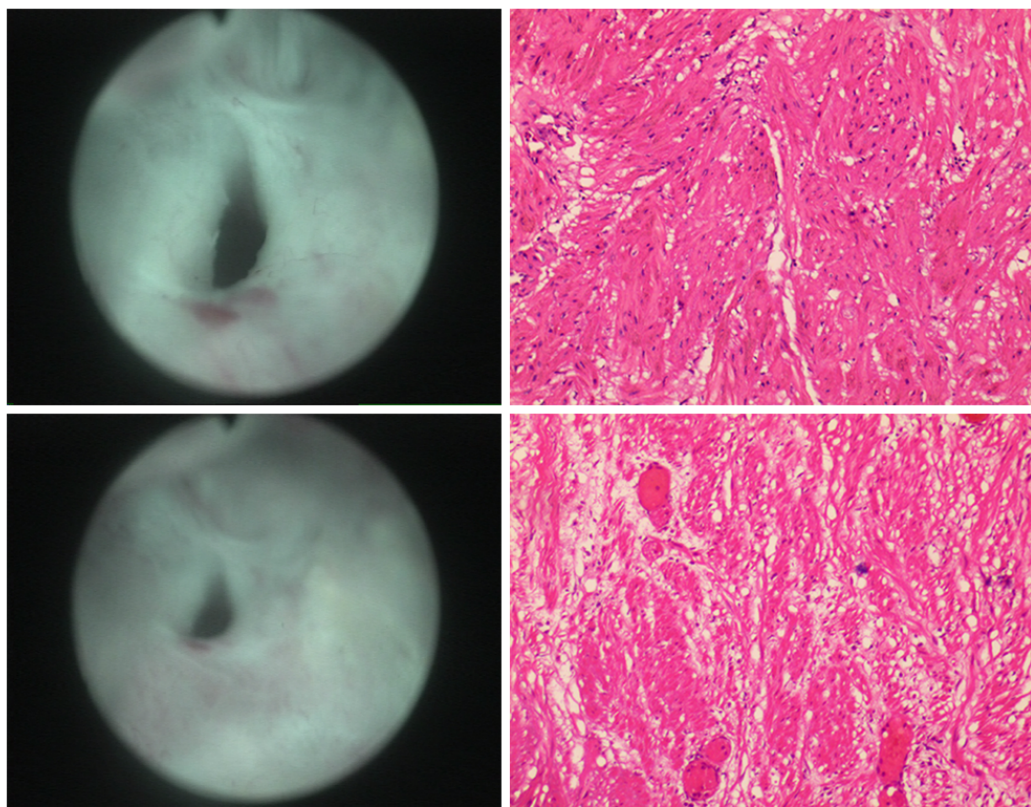


Figure 1. Cystoscopy and pathology

Chailing Decoction is a combination of two traditional Chinese herbal formulas, namely Xiaochaihu Decoction and Wuling Powder, which is used to alleviate various water retention and edema related to inflammation. Xiaochaihu Decoction consists of 7 herbs: Radix bupleuri, Radix scutellariae, Rhizoma pinelliae, Fructus jujubea, Radix ginseng, Rhizoma zingiberis recens and Radix glycyrrhizae. It is thought to have anti-inflammatory and anti-allergy effects and immunomodulating properties. Wuling Powder, which consists of Cortex cinnamomi, Rhizoma alismatis, Polyporus umbellatus, Poria and Radix atractylodis is thought to have diuretic effects[5]. In recent years, Chailing Decoction has been widely concerned by the scientific community because of its anti-inflammatory, immunomodulatory and anti-tumor properties[6]. Various studies have investigated how Chailing Decoction

affects the immune system. Chailing Decoction is believed to stimulate the corticotropin-releasing factor (CRF) neurons in the hypothalamus to increase the release of CRF, thus stimulating the synthesis and secretion of adrenocorticotropin (ACTH)[7]. Chailing Decoction has proved that it has the potential to promote steroid effects in treating immune disorders, stimulating the secretion of corticosteroids, increasing the number of steroid receptors and enhancing the effect of steroids on cells[8].

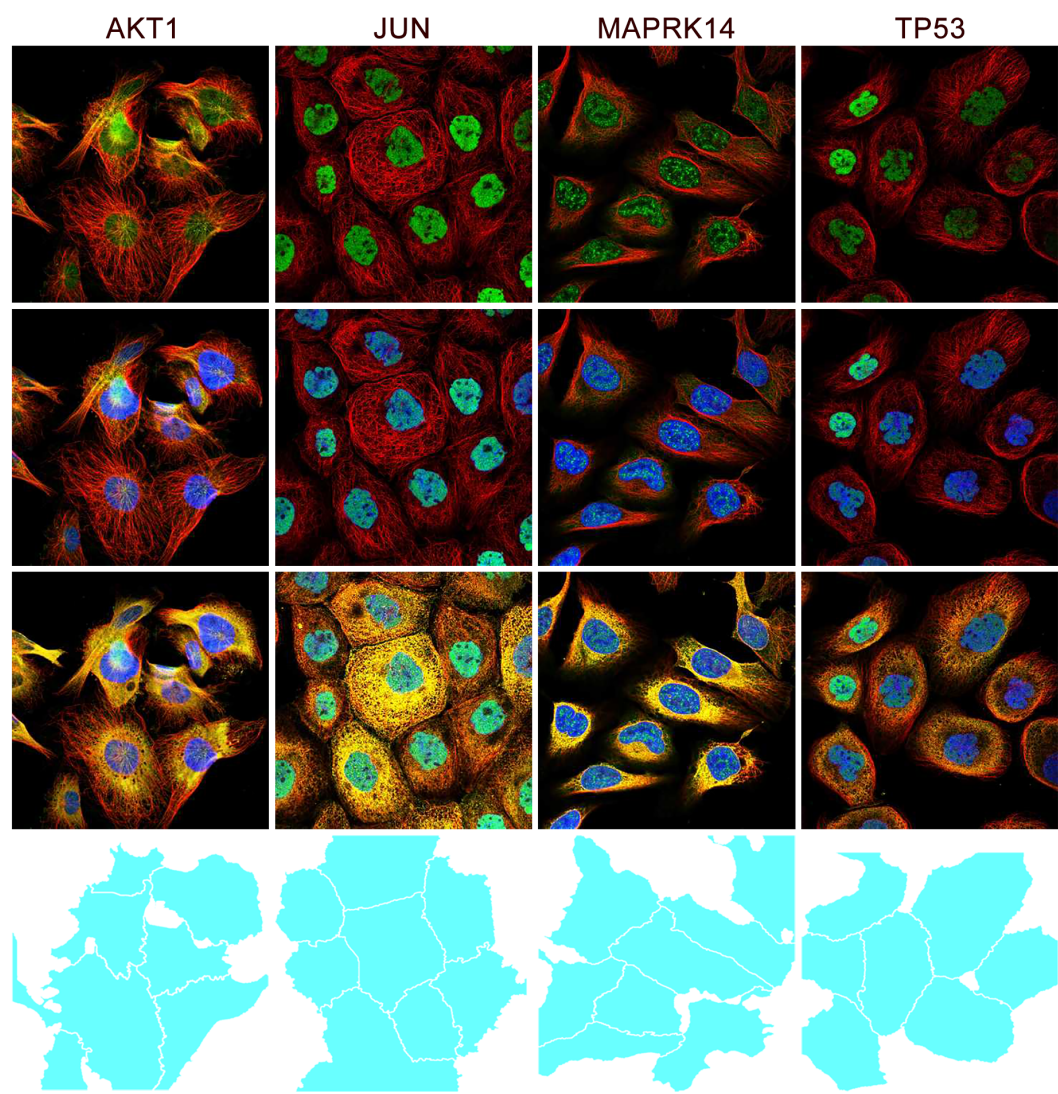


Figure 2. Immunofluorescence staining of four key target genes

The anti-inflammatory and scar-enhancing properties of corticosteroids on hypertrophic scars and keloids have been investigated and documented thoroughly. They are considered a first-line strategy in the treatment of limited keloidal and hypertrophic scars[9]. The most commonly used corticosteroid in this matter is triamcinolone acetonide, and its efficacy and

usefulness as well as its limitations are well known. Eltahawy et al. demonstrated a success rate of 83% after stricture site irrigation with triamcinolone following BNC ablation with a holmium laser[10]. Chailing Decoction reduces the inhibitory effect of prednisone (PSL) and accelerates the recovery of hypothalamus-pituitary-adrenal axis after PSL treatment[11]. In addition, Chailing Decoction itself may have immune regulation function, which is similar to that of corticosteroids in the treatment of immune dysfunction[12].

The drug-disease targets were obtained using publicly available databases. The analysis revealed 166 active compounds and 121 potential targets of Chailing Decoction from the pharmacological database of Chinese medicine system and analysis platform (TCMSP) and 3088 related targets of BNC from the GeneCards and Online Mendelian Inheritance in Man (OMIM) databases. Furthermore, 119 common targets of Chailing Decoction against BNC were identified, and these common targets were used to construct a protein-protein interaction (PPI) network. The visual PPI network was constructed by Cytoscape software. The top four genes from PPI according to degree value are AKT1, MAPK14, JUN, and TP53. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment were applied to reveal the potential targets and signaling pathways involved in Chailing Decoction against BNC, especially the lipid and atherosclerosis pathway. In addition, molecular docking revealed that baicalein, kaempferol, quercetin, wogonin, and formononetin displayed strong binding to AKT1, MAPK14, JUN, and TP53.

References

- [1] Chen YZ, Lin WR, Chow YC, Tsai WK, Chen M, Chiu AW. Analysis of risk factors of bladder neck contracture following transurethral surgery of prostate. *BMC Urol* 2021, 21(1): 59.
- [2] Lee YH, Chiu AW, Huang JK. Comprehensive study of bladder neck contracture after transurethral resection of prostate. *Urology* 2005, 65(3): 498-503; discussion 503.
- [3] Robinson HP, Greene LF. Postoperative contracture of the vesical neck. II. Experimental production of contractures in dogs: transurethral series. *J Urol* 1962, 87: 610-616.
- [4] Kaynar M, Gul M, Kucur M, Celik E, Bugday MS, Goktas S. Necessity of routine histopathological evaluation subsequent to bladder neck contracture resection. *Cent European J Urol* 2016, 69(4): 353-357.
- [5] Wang Z, Zhu L, Huang Y, Peng L. Successful treatment of immune-related cystitis by Chai-Ling-Tang (Sairei-To) in a gastric carcinoma patient: Case report and literature review. *Explore (NY)* 2022.
- [6] Kaburaki T, Zhang Q, Jin X, Uchiyama M, Fujino Y, Nakahara H, et al. Effects of Japanese herbal medicine Sairei-to on murine experimental autoimmune uveitis. *Graefes Arch Clin Exp Ophthalmol* 2013, 251(12): 2733-2739.
- [7] Hirako S, Tsuda H, Kotani T, Sumigama S, Mano Y, Nakano T, et al. Antenatal Saireito (TJ-114) Can Improve Pulmonary Hypoplasia and Pulmonary Vascular Remodeling

in Nitrofen-Induced Congenital Diaphragmatic Hernia. *Phytother Res* 2016, 30(9): 1474-1480.

- [8] Kurokawa I. Perifolliculitis capitis abscedens et suffodiens successfully treated with Saireito. *J Dermatol* 2019, 46(8): e299-e301.
- [9] Kant SB, van den Kerckhove E, Colla C, Tuinder S, van der Hulst RRWJ, Piatkowski de Grzymala AA. A new treatment of hypertrophic and keloid scars with combined triamcinolone and verapamil: a retrospective study. *European Journal of Plastic Surgery* 2017, 41(1): 69-80.
- [10] Eltahawy E, Gur U, Virasoro R, Schlossberg SM, Jordan GH. Management of recurrent anastomotic stenosis following radical prostatectomy using holmium laser and steroid injection. *BJU Int* 2008, 102(7): 796-798.
- [11] Fukunishi S, Nishida S, Nakamura K, Yokohama K, Ohama H, Asai A, et al. Co-Administration of Saireito Enabled the Withdrawal of Corticosteroids in an Elderly Woman with Autoimmune Hepatitis. *Intern Med* 2016, 55(1): 43-47.
- [12] Enomoto YM, Nakamura YMP, Enomoto NMP, Fujisawa TMP, Inui NMP, Suda T. Japanese herbal medicine-induced pneumonitis: A review of 73 patients. *Respir Investig* 2017, 55(2): 138-144.