Effectiveness of unani regimen in management of over active bladder: An open labelled, single arm clinical study

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ABSTRACT

Purpose: To study the efficacy of Unani pharmacopoeial formulations viz Jawarish Zarooni, Majoon Kundur and Arq e Badiyaan as a treatment regimen in patients of overactive bladder and evaluate its effect on their quality of life.

Materials and Method: This open labeled, single arm clinical study was conducted at Regional Research Institute of Unani Medicine (RRIUIM), Srinagar. Patients fulfilling the inclusion criteria were enrolled in the study after signing the informed consent form. Jawarish Zarooni and Arq e Badiyaan were prescribed orally in the dosage of 7 g and 30 ml respectively twice a day along with 7 g single oral dose of Majoon Kundur. The duration of treatment was for 82 days. The patients were followed up on first, fourth, eighth and twelfth week. The results were expressed as Mean ± SEM. Symptomatic relief was assessed as percentage change in terms of presence of any symptom at baseline and at 82nd day.

Results: Of the 36 patients enrolled 31 patients completed the study. The study demonstrated highly significant results (p<0.001) for nocturia and QOL as measured by patients perception of bladder control (PPBC), urinary incontinence and daytime micturation whereas very significant results were observed (p<0.01) for urgency.

Conclusions: The Unani regimen was highly effective in managing the symptoms of OAB as the regimen has an array of phyto-constituents which demonstrated muscarinic antagonism, Ca2+ channel blocking, K channel opening, neuro-protection, neuro-toning and anxiety relieving properties. About 50% of the ingredients of the regimen were Ca2+ blockers. The synergism of these phyto-constituents probably made Ca2+ blockers effective in OAB.

Keywords: Over Active Bladder, Ca2+ blocker, antimuscaranics

INTRODUCTION

Overactive Bladder (OAB) is a syndrome that includes urinary urgency with or without urge incontinence, voiding frequency of eight or more times per 24 hours and nocturia (voiding more than two times at night).1 Normal bladder contraction during voiding involves stimulation of the muscarinic receptors on the detrusor muscle by acetylcholine.2 Distended bladder activates voltage-gated channels and a large increase in Ca2+ results in detrusor contraction and bladder emptying.3

During bladder pathology, muscarinic receptor changes occur in the detrusor.4 Partial denervation of the detrusor alters the smooth muscles leading to increased excitability and increased ability of activity to spread between cells, resulting in coordinated myogenic contractions of the whole detrusor.5 Hence, muscarinic antagonists remain the mainstay of treatment for the overactive bladder (OAB).7 The adverse effects of muscarinic antagonists like mydriasis (causes blurred vision), tachycardia, agitation, urinary retention, and delirium8 have prompted many studies for a safer and more tolerable treatment option.

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Also the symptoms of OAB are associated with significant social, psychological, occupational, domestic, and physical stigmas. It affects traveling, physical activity, relationships, sexual function, and nocturnal bladder control, and even sleep.6

In light of the above, the present clinical study was conducted to evaluate the efficacy of a time tested regimen of Unani pharmacopoeial formulations viz. Jawarish Zarooni, Majoon Kundur and Arq e Badiyaan in OAB and to study their impact on the quality of life of the patients in an open labeled, single arm clinical study.

MATERIAL AND METHODS

The study was carried at Regional Research Institute of Unani Medicine (RRIUM), Srinagar, India with the objective to evaluate the safety and efficacy of a Pharmacopoeial Unani regimen and to study its effect on the quality of life. The study was an open-labeled single-arm clinical trial. The trial was cleared by the institutional ethical committee of RRIUM, Srinagar thereafter it was registered at Clinical Trial Registry of India (CTRI) bearing registration No. REF/2014/11/007887. During the trial GCP guidelines and declaration of Helsinki were adhered to.

Patients were enrolled if they satisfied the following inclusion criteria. Patients aged 18 yrs to 60 yrs of either gender giving a history of urinary urgency and incontinence for more than six months were included in the study. Patients having renal calculus, UTI, BPH, uterine prolapse, Rectocele/cystocele, cystitis, DM, HT, Hepatic/Cardiac diseases, Multiple sclerosis and Spinal cord injury were excluded from the study. So were pregnant and lactating mothers.

The regimen is a combination of three Unani Pharmacopoeial herbal formulations viz. Jawarish Zarooni (sugar based semisolid formulation containing drugs mentioned in Table 1).

| Botanical name                  | Name of Drug            | Quantity |
|--------------------------------|-------------------------|----------|
| Seeds of Daucus carota Linn.   | Tukhm Gazar             | 30 g     |
| Seed of Apium graveolens Linn. | Tukhm Karafs            | 30 g     |
| Seeds of Trifolium alexandrinum Linn. | Tukhm Ispust       | 30 g     |
| Trachyspermum ammi (Linn.) Spraghe | Nankhawh           | 30 g     |
| Foeniculum vulgare Mill.       | Badiyan                 | 30 g     |
| Cotyledons of Cucumis melo Linn. | Maghz Tukhm Kharbuza   | 30 g     |
| Cotyledons of Cucumis sativus L. | Maghz Tukhm Khayarain  | 30 g     |
| Root bark of Apium graveolens Linn. | Post heilh karafs     | 30 g     |
| Piper nigrum, Linn.             | Filfil siyah            | 30 g     |
| Anacyclus pyrethrum DC.         | Aqarqarha               | 10 g     |
| Cinnamomum zeylanicum Blume     | Darchini                | 10 g     |
| Crocus sativus, Linn.           | Zafran                  | 10 g     |
| Pistacia lentiscus Linn.        | Mastagi                 | 10 g     |
| Aquilaria malaccensis Lam. Syn.: A. agallocha Roxb. | Ood hindi | 10 g |
| Myristica fragrans Houtt.       | Bisbasa                 | 10 g     |
Table 2: Constituent of Majoon Kundur

| Botanical name                              | Name of Drug | Quantity |
|---------------------------------------------|--------------|----------|
| Pistacia lentiscus Linn.                    | Mastagi      | 100 g    |
| Boswellia serrata Roxb. ex Coleb.           | Kundur       | 100 g    |
| Asplenium adiantum nigrum                   | Baloot       | 100 g    |
| Flowers of Punica granatum Linn.            | Gulnafarsi   | 100 g    |
| Nigella sativa Linn.                        | Kalongi      | 100 g    |
| Dried seeds of Coriandrum sativum Linn.    | Kishneezkhushk | 100 g  |
| Carum carvi Linn.                           | Zeera siyah  | 50 g     |
| Trachyspermum ammi (Linn.) Spragne          | Nankhawh    | 50 g     |
| Rind of Terminalia bellirica (Gaertn.) Roxb.| Post Balela | 30 g     |
| Terminalia chebula Retz.                    | Halela zard  | 30 g     |
| Terminalia chebula Retz.                    | halela siyah | 30 g     |
| Phyllanthus emblica Linn. Syn.: Emblica officinalis Gaertn. | Amla | 30 g     |

Majoon Kundur (sugar based semisolid preparation containing drugs mentioned in Table 2) and Arq e Badiyaan (Fennel seeds distillate) and to be taken orally for 82 days. The dosage of these drugs was Jawarish Zarooni 7 g twice daily, Arq e Badiyaan 30 ml twice daily and Majoon Kundur 7 g in the morning. Duration of protocol therapy was 12 weeks with follow-up at 4th, 8th and 12th week.

Of the 36 patients enrolled 31 completed the study. One patient dropped because his symptoms aggravated, three patients were lost in follow up and one patient reported inability to continue due to unpleasant taste of the drug.

Assessment of efficacy was done on Urgency Urinary Incontinence scale (UUI), Urgency Perception Scale (UPS), Change in the number of nocturnal micturation, and Patient Perception of Bladder Condition scale (PPBC) before, at each follow-up and after completion of protocol therapy. Whereas, safety was assessed on clinical and biochemical parameters before and after the protocol therapy. Liver function test and kidney function test were conducted before and after the study to record the safety and tolerability of the test regimen. Safety was assessed clinically by absence of any adverse event reporting.

Statistical analysis

Before Treatment and After Treatment values of clinical subjective parameters, pathological and biochemical parameters were statistically analyzed using student’s paired ‘t’ test. The result was expressed as the Mean ± SEM. Symptomatic relief was assessed as percentage change in terms of presence of any symptom at baseline and at 12th Week. The obtained results were interpreted as statistically significant as p<0.05, p<0.01 and highly significant as p<0.001.

Data are available for bona fide researchers who request it from the authors.
Figure 3: Chronicity of disease wise distribution of the patients

Table 4: Socio-economic Status wise distribution of the patients

| Socio-economic Status | Number of Cases | Percentage (%) |
|-----------------------|-----------------|----------------|
| Lower                 | 14              | 45.16          |
| Middle                | 16              | 51.61          |
| Higher                | 1               | 3.23           |
| Total                 | 31              | 100            |

Figure 4: Socio-economic Status wise distribution of the patients
Table 5: Effect of drugs on clinical parameters

| Clinical Parameters                      | Follow-ups | Mean ± S.E.M | Percentage Improvement over BL (%) | p-value |
|------------------------------------------|------------|--------------|------------------------------------|---------|
| Urgency Urinary Incontinence             | BL         | 3.35 ± 0.14  | 17.31%                             | <0.001  |
|                                          | EL         | 2.77 ± 0.18  |                                    |         |
| Urgency Perception Scale                 | BL         | 2.00 ± 0.11  | 19.50%*                            | <0.01   |
|                                          | EL         | 2.39 ± 0.13  |                                    |         |
| Patient Perception of Bladder Condition  | BL         | 4.06 ± 0.23  | 18.23%                             | <0.001  |
|                                          | EL         | 3.32 ± 0.21  |                                    |         |
| Change in n.o. of micturation/24hrs      | BL         | 12.23 ± 0.56 | 25.59%                             | <0.001  |
|                                          | EL         | 9.10 ± 0.58  |                                    |         |
| Change in n.o. of nocturnal micturation  | BL         | 2.37 ± 0.22  | 42.19%                             | <0.001  |
|                                          | EL         | 1.37 ± 0.29  |                                    |         |

* Percentage Improvement over EL (%) (Since in this scale the more the score the better the symptoms)

BL- Base line; EL – End line

1. Urgency Urinary Incontinence: 1-no urgency, 2-mild, 3-moderate, 4-severe, 5-incontinence
2. Urgency Perception Scale: 1-not able to hold urine, 2-hold but hurry, 3-hold until finish
3. Patient Perception of Bladder Condition: 1-bladder does not cause problem, 2-bladder cause very minor problem, 3-bladder cause minor problem, 4-bladder cause moderate problem, 5-bladder cause severe problem

Table 6: Effect of drugs on pathological and biochemical parameters

| Name of Parameter                  | Mean ± S.E.M | Range | Percentage of Increase (↑) / Decrease (↓) | Paired 't' test |
|------------------------------------|--------------|-------|------------------------------------------|----------------|
|                                    | Before       | After  | Before       | After          | Statistic value | P-value |
| S.Bilirubin (mg/100 ml)            | 0.44 ± 0.06  | 0.57 ± 0.06 | 0.1-1.0 | 0.1-1.2         | 22.81 ↑        | -2.16 <0.05 |
| SGOT (IU/L)                        | 21.41 ± 2.01 | 20.13 ± 1.34 | 5-65    | 2-31           | 5.98 ↓         | 0.58 0.56 |
| SGPT (IU/L)                        | 22.15 ± 1.63 | 17.86 ± 1.27 | 10-46   | 7-30           | 19.38 ↓        | 2.53 <0.05 |
| S.Alkaline Phosphatase (IU/L)      | 92.68 ± 7.11 | 69.54 ± 6.2  | 37-218  | 16-170         | 4 ↑            | -0.44 0.65 |
|                                    |              |         |       |                |                 |         |
| S.Creatinine (mg/100 ml)           | 0.67 ± 0.06  | 0.57 ± 0.06 | 0.1-1.4 | 0.1-1.2         | 14.33 ↓        | 1.53 0.13 |
| S.Urea (mg/100 ml)                 | 24.57 ± 0.81 | 25.03 ± 0.94 | 20-39   | 20-38          | 1.85 ↑         | -0.47 0.64 |
| S. Uric Acid (mg/dL)               | 5.13 ± 0.08  | 4.4 ± 0.09  | 4-6     | 4.4-6.4        | 2.24 ↑         | -0.95 0.34 |
| Blood Sugar Fasting                | 85.17 ± 2.4  | 86.8 ± 2.13 | 70-110  | 68-110         | 1.87 ↑         | -0.73 0.47 |
| Blood Sugar Post Prandal           | 114.98 ± 2.81 | 120.28 ± 2.85 | 92-148  | 98-150         | 4.4 ↑          | -1.94 0.06 |

DISCUSSION

Although OAB can affect anyone at any age, the prevalence tends to increase with advancing age. It was observed during the study that postponing micturation frequently over a period of time too attributes to urge incontinence. A study in 2012 by Smith P.P et al concludes that aging is associated with an impaired ability to respond to the challenge of continuous bladder filling with cyclic voiding and that changes in homeostatic reserve and peripheral and/or central sensory mechanisms may be important contributors to aging-associated changes in bladder function. Thus our results are in cohesion with the results of this study wherein
highest number of patients registered were of 39.71 ± 2.18 age.

Studies suggest that OAB and urge incontinence are more common in women especially at times of changing hormonal levels.13 Hormonally induced differences in neurotransmitter systems (eg, by 5-HT) may explain this sexual difference in OAB in the nonelderly.14 The incidence in our study seems to be more in women with a mean history of 22.58 ± 1.86 months probably because women tend to have a weak pelvic floor from child birth. A meta analysis on 794 patients of OAB from 10 studies by Yuwei Zhao had 590 women and 84 men wherein women outnumbered men by 63.7%.15

The perception of the patient on their control on urgency as measured by perception of bladder control scale (PPBC) was highly significant p <0.001 with an 18.23% improvement over BL and Urgency perception scale (UPS) was very significant p <0.01 with an 19.50% improvement over EL. This was perhaps due to the fact that the patients were under a lot of stress from this social embarrassing disorder for around a year. Aging is associated with diminished volume sensitivity as has been demonstrated by Smith et al.12 This is consonant to our finding.

The most disturbing symptom of OAB was polyuria followed by urinary urgency, urgency incontinence, and nocturia.16 However, urgency is considered as the incidence of OAB.15 According to our study, the most annoying symptom faced by the patients was of urgency leading to incontinence. The effect of the regimen on UUI scale was highly significant p <0.001 with 17.31% improvement over BL. The effect on micturation as measured by 24 hrs micturation and nocturia was highly significant p <0.001 with 25.59% and 42.19% improvement over BL respectively.

The regimen acted on multiple targets through its active phyto-constituents like:

1. **Antimuscarinics**: Antimuscarinics inhibit binding of acetylcholine at muscarinic receptors M(2) and M(3) on detrusor smooth muscle cells and other structures within the bladder wall.17 32% of the constituents of the regimen are antimuscarinics in their effect as seen in table 7.

2. **Ion Channels**: Contractions of human detrusor not only depend on calcium entry through L-type calcium channels but can also modulate them.23 Thus, an increasing conductance through K(ATP), BK(Ca2+) and SK(Ca2+) channels may decrease phasic contractions of detrusor smooth muscle in OAB.24 Calcium antagonists and potassium channel openers both offer another target to prevent bladder excitation.4 48% of the constituents of the regimen have direct impact on the ion channels as is evident from studies in table 7.

3. **Neuro tonic**: These drugs strengthen the nervous tissue. 12% of the constituents of the regimen have proven neurotonic properties.

4. **Anxiolytics**: These relieve the stress. 20% of the constituents are anxiolytics with definite proof as is evident in table 7.

| Name of drug            | Active Constituent                  | Mode of action                                           | Ref |
|-------------------------|-------------------------------------|----------------------------------------------------------|-----|
| **Antimuscarinics**     |                                     |                                                          |     |
| Jawarish Zaruni         |                                     |                                                          |     |
| Celery (Apium graveolens) | Flavonoids                          | muscarinic receptor antagonist on smooth muscle          | 18  |
| Saffron (Crocus sativa) | Safranal                            | functional antagonist on muscarinic receptors            | 20  |
| Carrot (Daucus Carota)  | Cumarin glycosides coded as DC-2 and DC-3 | Inhibited K+ induced contractions                     | 40,43|
| Pistacia lentiscus      | Ethanolic extract                   | inhibits the activity of acetylcholine                   | 42  |
| **Majoon Kundur**       |                                     |                                                          |     |
| Boswellia (Boswellia Serrata) | 3-acetyl-11-keto-β-boswellic acid | L-type Ca2+ channels                                    | 19  |
| Punica granatum         | Saponins                            | inhibits acetylcholine contractions                      | 21  |
| Nigella sativa          | Thymoquinone and other constituents of volatile oil | counters the contractions of acetylcholine              | 31  |
| Arq Badiyan             |                                     |                                                          |     |
| Fennel (Foenaculm vulgare) | Essential oil                      | muscarinic inhibitory at EC_{50} of 162.33 ± 96.36       | 33  |
| **Ion Channels**        |                                     |                                                          |     |
| Jawarish Zaruni         |                                     |                                                          |     |
| Myristica fragrans      | Hot aqueous extract                 | Ca channel blocker                                       | 25  |
| Trachyspermum ammi      | Thymol                              | Ca channel blocker                                       | 26  |
| Piper nigrum            | Piperine                             | blockage of voltage-dependent calcium channels          | 27  |
| Cinnamomum zeylanicum   | Ethnolic extract                    | limits calcium influx through inhibition of L-type       | 28  |
Ca(2+) channels

**Apium Graveolens**
- Apigenin or extracts of dichloromethane, ethyl acetate extracts
- block voltage-dependent and receptor operated Ca\(^{2+}\) channels
- 33, 35

**Carrot (Daucus carota)**
- Cumarin glycosides coded as DC-2 and DC-3
- blockade of calcium channels
- 40, 43

**Crocus sativus**
- Safarnal
- \(\text{Ca}^{2+}\) influx through receptor-operated Ca\(^{2+}\) channels and potential-dependent Ca\(^{2+}\) channels
- 29

**Punica granatum**
- Saponins
- inhibits voltage gated calcium channels at EC\(_{50}\) 8.6 ± 1 mg/ml
- 21

**Carum carvi**
- Carvone
- blocker of voltage dependent Ca channels
- 30

**Coriandrum sativum**
- Fatty aldehyde (E)-2-dodecenal
- Activates multiple KCNQs in EC\(_{50}\) 60 ± 20 nM.
- 32

**Arq Badiyan**

- **Neuro tonic**
- Cuminum carvi
- Carvone
- blocker of voltage dependent Ca channels
- 30

- **Anxiolytics**
- Boswellia (Majoon Kundur)
- Incensole acetate
- neuro-protective, neuro tonic; anti-depressive and anti-anxiolytic
- 37

- **Majoon Kundur (Per say)**
- -
- *Muqawwi Aasab* (nerve tonic)
- 11

- **Celery (Apium graveolens)**
- Jawarish Zaruni
- Essential oil
- nervine tonic; reduces distress and irritation of nervous system
- 35

- **Anacyclus pyrethrum**
- Ethanolic extract
- tonic to the nervous system
- 41

- **Majoon Kundur (Per say)**
- -
- *Habis* (retentive or anti-secretory i.e. it works on the smooth muscles)
- 11

- **Fennel (Foeniculum vulgare)**
- Aqueous extract of dried fruit
- inhibits stress induced urinary biochemical changes in rats
- 39

- **Anacyclus pyrethrum**
- Ethanolic root extract
- antidepressant effect
- 41

There has been no significant change in biochemical and pathological parameters. The drug has significant lowering effect on SGPT (p<0.05). However the SGPT levels did not fall below the normal range. Two drugs of the regimen were sugar based hence there has been increase in post prandial blood sugar values however these changes were not significant. Though serum bilirubin was raised significantly (p<0.05); however the S. bilirubin levels did not rise below the normal range.

**CONCLUSION**

Our study demonstrated that OAB, a disease associated with ageing is now more prevalent in middle aged women and they seek help after a mean period of approx 1 yr. The reason could be social, financial or pure laze.

The present study proved effective in controlling urgency, polyuria and quality of life. Stress which aggravated and magnified the problem too was constrained down with this regimen.

The myriad bio-molecules of the regimen addressed different pathways of OAB giving a holistic response. These were achieved without any unwarranted effects as is observed by the main stay drugs for OAB. However the effect of the regimen on Serum bilirubin does need to be studied.

The hitherto skeptical role of calcium channel blockers when coupled with anti muscaranics and neuro protective molecules have yielded good results. In the light of this study it can be inferred that Calcium inhibitors can be given a chance in OAB management as an adjuvant. However this needs to be explored further.

Another conclusion that can be drawn from the study is that the role of herbal muscaranics cannot be undermined and should be explored to their full potential.

**Limitation**

The sample size was too small besides the results achieved were from a regimen of three polyherbal drugs. A study on the precise effect of each drug and to what extent, on a bigger sample size would give more accurate and conclusive results.

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Conflict of Interest

The authors declare no conflict of interest whatsoever.

REFERENCES:

1. Joseph G. Ouander; Management of Overactive Bladder; N Engl J Med 2004; 350:786-799.
2. Athanasopoulos A, Giannitsa K; An Overview of the Clinical Use of Antimuscarinics in the Treatment of Overactive Bladder; Advances in Urology; 2011; Article ID 820816, 8 pages.
3. William Steers, Potential Targets in the Treatment of Urinary Incontinence; Rev Urol 2001; 3(Suppl 1):S19–S26.
4. Giglio D, Tobin G; Muscarinic receptor subtypes in the lower urinary tract; Pharmacology 2009; 83(5):259-69.
5. Alison F. Bradling; A myogenic basis for the overactive bladder; Urology; 1997; 50(6):57-67.
6. Wein AJ, Rivner ES; The overactive bladder: An overview for primary care health providers. Int J Fertil 1999; 44:56-66.
7. Sellers DJ, Chess-Williams R; Muscarinic agonists and antagonists: effects on the urinary bladder; Handb Exp Pharmacol 2012; (208):375-400. doi: 10.1007/978-3-642-42274-9_16.
8. Mark Kester, Kelly D. Karpa and Kent E. Vrana; Elsevier's Integrated Review Pharmacology (Second Edition); Chap 6 - Autonomic Nervous System; 2012.
9. Anonymous; NFUM; CCRUM, New Delhi; Vol I; pg 106.
10. Anonymous; NFUM; CCRUM, New Delhi; Vol I; pg 214.
11. Anonymous; NFUM; CCRUM, New Delhi; Vol I; pg 106-107.
12. Anonymous NFUM; CCRUM, New Delhi; Vol I; pg 133.
13. Smith P.P, DeAngelis.A, Kuchel G.A, 2011, Detrusor expulsive strength is preserved, but responsiveness to bladder filling and urinary sensitivity is diminished in the aging mouse; aging 2011; 3(2):577-586.
14. Archer JS; NAMS/Solvay Resident Essay Award. Relationship between estrogen, serotonin, and depression; Menopause. 1999; 6(1):71-81.
15. William D Steers; Pathophysiology of Overactive Bladder and Urge Urinary Incontinence; Rev Urol 2002; 4(Suppl 4):S71–S86.
16. Mitchell SA, Brucker BM, Kaefer D, et al. Evaluating patients' symptoms of overactive bladder by questionnaire: the role of urgency in urinary frequency. Urology 2014; 84:1039–43.
17. Abrams P, Andersson KE; Muscarinic receptor antagonists for overactive bladder; BJU Int. 2007; 100(5):987-1006.
18. Marija Gočmanac Ignjatović , Dušanka Kitić, Marija Kostić, Bojana Miladinović, Milica Milutinović, Milica Veljković, Suzana Branković; Spasmolytic Effect of Anethum Graveolens L. Methanol Extract On Isolated Rat Ureth. Acta Medica Mediterranea 2015; 54(2):5-10.
19. Borrelli F, Capasso F, Capasso R, Ascione V, Aviello G, Longo R, Izzo A.A; Effect of Boswellia serrata on intestinal motility in rodents: inhibition of diarrhoea without constipation; British Journal of Pharmacology 2006; 148:553-560.
20. Neamat, N Boskabady MH. Effect of Crocus sativus (saffron) on muscarinic receptors of guinea pig tracheal chains. Func Plant Sci Biotechnol 2010; 4:128-131.
21. Ali N, Ayeha Jamil, Syed Wadood Ali Shah, Ismail Shah & Ghayour Ahmed; Spasmogenic and spasmylic activity of rind of Punica granatum Linn; BMC Complementary and Alternative Medicine 2017; 17, Article number: 97.
22. Zaer AM, Khazdair MR and Boskabady MH; Smooth muscle relaxant activity of Crocus sativus (saffron) and its constituents: possible mechanisms; Avicenna J Phymomed. 2015; 5(2):365–375.
23. Darblade B, Behr-Roussel D, Oger S, et al: Effects of potassium channel modulators on human detrusor smooth muscle myogenic phasic contractile activity: potential therapeutic targets for overactive bladder. Urology 2006; 68:442–448.
24. Cerruto M.A, Asimakopoulos A.D, Artibani W, Del Popolo G, La Martina M, Carone R, Finizzi-Agré E; Insight into New Potential Targets for the Treatment of Overactive Bladder and Detrusor Overactivity; Urol Int 2012; 89:1-8.
25. Ichikawa K, Kinosita A, Sakawa U; The Screening of Chinese Crude Drugs for Ca2+ Antagonistic Activity: Identification of Active Principles from Aerial Parts of P.cablin and Fruit of P. mume; Chem. Pharm. Bull. 1989; 37(2):345-348.
26. Aftab K, Atta-ur-Rahman, Usmanghani K; Blood pressure lowering action of active principle from Trachyspermum ammi (L.) Sprague; Phytotherapy Research 1995; 9(3):35-40. doi: 10.1016/S0944-7113(1)80046-2.
27. Hilavcova L, Urbanova A, Ulcina O, Janega P, Cerna A, Babal P; Piperine, active substance of black pepper, alleviates hypertension induced by NO synthesis inhibition; Bratisl Lek Listy. 2010; 111(6):426-31.
28. Ranasinge P, Piqera S, Premakumara GAS, Galappathy P, Constantine GR, and Katulanda P; Medicinal properties of ‘true’ cinnamon (Cinnamomum zeylanicum): a systematic review; BMC Complement Altern Med. 2013; 13: 275.
29. Razavi BM, Amanloo MA, Imsesahidi M, Hosseinazzadeh H; The Relaxant Activity of Safarnal in Isolated Rat Aorta is Mediated predominantly via an Endothelium-Independent mechanism- Vasodilatory Mechanism of Safarnal; J Pharmacopuncture. 2016; 19(4):329–335.
30. Keshavarz A, Minaijan M, Ghannadi A, and Mahzouni P; Effects of Carum carvi I. (Caraway) extract and essential oil on TNBS-induced colitis in rats; Res Pharm Sci. 2013; 8(11):1-8.
31. Keyhanmamr esh R, Gholamnezadz Z, and Boskabady MH; The relaxant effect of Nigella sativa on smooth muscles, its possible mechanisms and clinical applications; Iran J Basic Med Sci 2014; 17(12):939-949.
32. Manville RW, Abbott GW. Gliant leaf harbors a potent potassium channel-activating anticonvulsant. The FASEB Journal, 2019; R164, DOI: 10.1007/164.
33. Jorge VG, Luis Ángel JR, Adrián TS, Francisco AC, Anuar SG, Samuel ES, Ángel SO, Emmanuel HN; Vasorelaxant activity of extracts obtained from Apium graveolens: Possible source for vasorelaxant molecules isolation with potential antihypertensive effect; Asian Pac J Trop Biomed. 2013; 3(1):776-779.
34. Boskabady MH, Khatami A, Nazari A; Possible mechanism(s) for relaxant effects of Fenocium vulgare on guinea pig tracheal chains; Pharmazie. 2004; 59(7):561-4.
35. Kooti W, Akbari S.A, Samani M.A, Ghadery H, Larky DA, A Review on Medicinal plant of Apium graveolens; Advanced Herbal Medicine 2015; 1(1):48-59.
36. Coyne KS, Sexton CC, Kopp ZS, et al. The impact of overactive bladder on mental health, work productivity and health-related quality of life in the UK and Sweden: results from EpilJITTS. BJU Int.2011; 108:1459–71.
37. Moussaiell A, et al. Incensole acetate: a novel neuroprotective agent isolated from Boswellia carteri. J Cereb Blood Flow Metab 2008; 28:1341–1352.
38. Sushruta Koppula and Hemant Kumar; Fenocium vulgare Mill (Uncibiferae) Attenuates Stress and Improves Memory in Wistar Rats. Tropical Journal of Pharmaceutical Research 2013; 12 (4):553-558.
39. M.H. Boskabady & A. Khatami, Relaxant Effect of Fenocium vulgare on Isolated Guinea Pig Tracheal Chains, Pharmaceutical Biology, 2003; 41(3):211-25.
40. Gilani AH, Shaheen E, Saeed SA, Bibi S, Irfanullah, Sadiq M, et al. Hypotensive action of coumarin glycosides from Daucus carota. Phytomedicine 2000; 7:423–6.
41. Aboufatima Rachida, Mountsair Maryam, Khalil Hanane, Fereha Hind, Farouk Loubna, Chigier Fatma, Najmi Mohamed, Zayed Abdelmajid, Chait Abderrahman; Scopolamine-Induced Impairment in Copulation and Exploratory Behaviours is Enhanced by Anacyclus Pyrethrum. Tropical Journal of Pharmacy & Biotechnology 2009; 3(1):176-179.
42. Gholamali Naderi, Mehrdad Roghani; A study on inhibitory effect of ethanolic extract of the Pistacia lentiscus on smooth muscles of guinea pigs; J Ethnopharmacol 2006; 107(2):245-50.
43. Siddiqui AA, Wani SM, Rajesh R, Alagarsamy V; isolation and hypotensive activity of three phytoconstituents of seeds of Daucus carota; Indian J pharm Sci; 2005; 67 (6):716-720.