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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 (RRIUM), 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 7g and 30 ml respectively twice a day along with 7g 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 muscuranic antagonism, Ca^{2+} channel blocking, K channel opening, neuro-protection, neuro-toning and anxiety relieving properties. About 50% of the ingredients of the regimen were Ca^{2+} blockers. The synergism of these phyto-constituents probably made Ca^{2+} blockers effective in OAB.

Keywords: Over Active Bladder, Ca^{2+} blocker, antimuscuranics

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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 Ca^{+2} 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 muscuranic antagonists like mydriasis (causes blurred vision), tachycardia, agitation, urinary retention, and delirium[8] have prompted many studies for a safer and more tolerable treatment option.

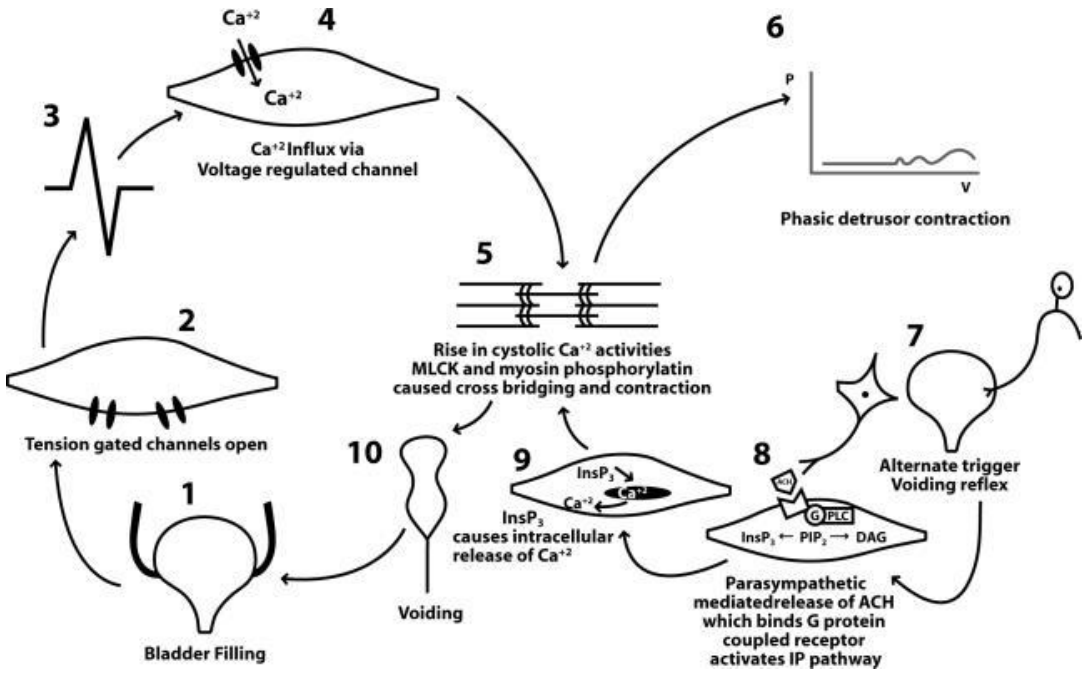

Figure 1: Illustrating the mechanism of micturation[4].

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),[9]

Table 1: Constituent of Jawarish Zarooni [9]

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.) Spragne	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 beikh 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[11]

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.	Gulnar farsi	100 g
Nigella sativa Linn.	Kalongi	100 g
Dried seeds of *Coriandrum sativum* Linn.	Kishneez khushk	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)[11] and *Arq e Badiyaan* (Fennel seeds distillate)[10] and to be taken orally for 82 days. The dosage of these drugs was *Jawarish Zarooni* 7g twice daily, *Arq e Badiyaan* 30ml 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 daytime micturation, Change in 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.

RESULTS

Table 3: Gender & Age of Patients and Chronicity of Disease

S. No.	Characteristics	Number of Cases
1.	Male	11 (35%)
	Female	20 (65%)
	Total cases	31
2.	Age (Mean ± SEM)	**39.71 ± 2.18**
	Age (Range)	18 – 60
3.	Chronicity (Median ± SEM)	22 ± 1.86
	Chronicity (Range)	1 – 48 (month)

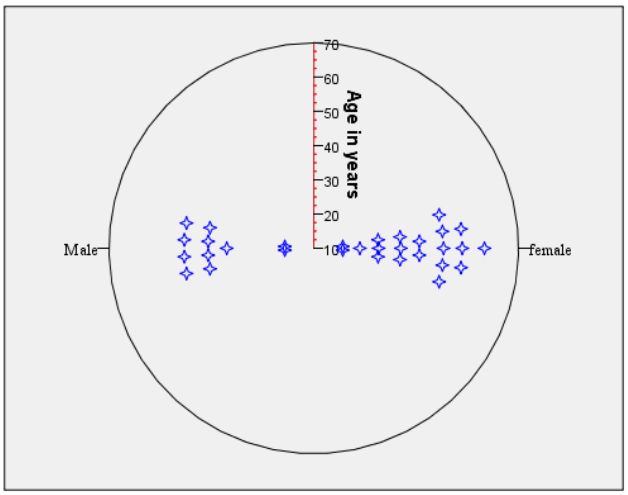

Figure 2: Age and Sex-wise Distribution of Patients

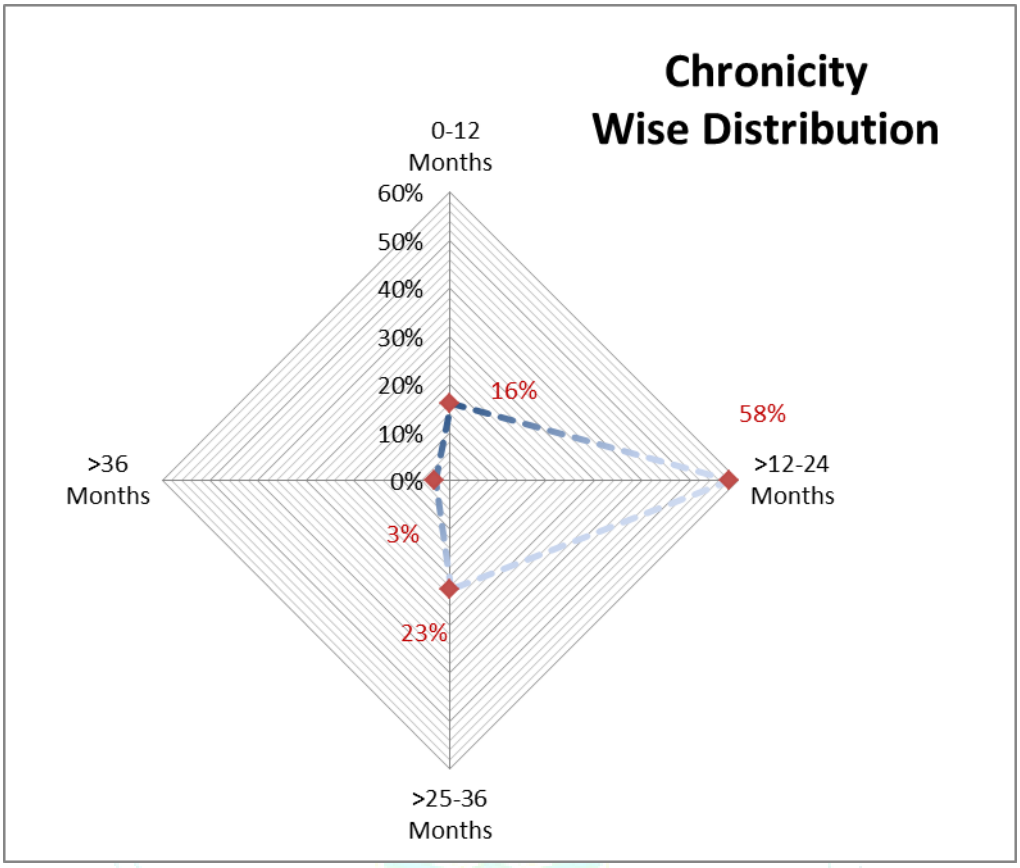

Figure 3: Chronicity of disease wise distribution of the patients

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**

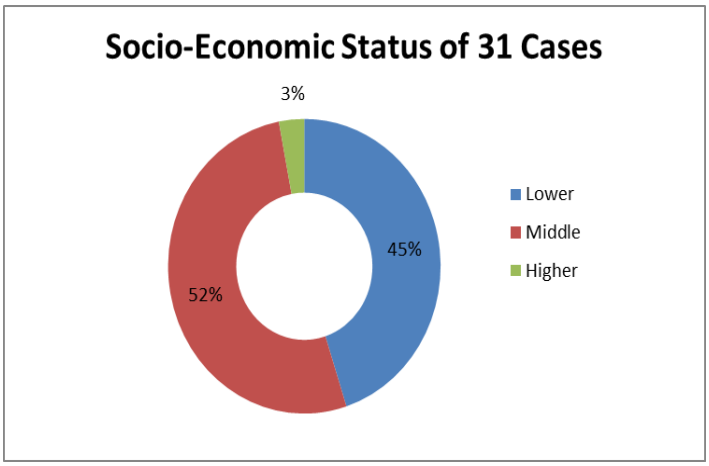

Figure 4: Socio-economic Status -wise distribution of the patients

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 no. of micturation/24hrs	BL	12.23 ± 0.56	25.59%	<0.001
	EL	9.10 ± 0.58		
Change in no. 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 Treatment	After Treatment	Before Treatment	After Treatment			Statistic value	P-value
LFT	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
KFT	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[2,5]. 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.[12] 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 an19.50% 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 brand symptom 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 *5.* 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 antimuscuranics 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.

Table 7: Possible mode of Action of Drugs

Name of drug	Active Constituent	Mode of action	Ref
Antimuscuranics			
Jawarish Zaruni			
Celery (Apium graveolens)	Flavonoids	muscaranic receptor antagonist on smooth muscle	18
Saffron (Crocus sativa)	Safarnal	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 Ca^{2+} 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	34
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
Majoon Kundur			
Crocus sativus	Safarnal	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			
Fennel (*Foenaculm vulgare*)	Essential oil	potassium channel opening and Ca channel antagonistic	34, 39
Neuro tonic			
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)	-	*Muqawwi Aasab* (nervine tonic)	11
Anxiolytics			
Boswellia (*Majoon Kundur*)	Incensole acetate	neuro-protective, neuro tonic, anti-depressive and anti- anxiolytic	37
Majoon Kundur, (Per say)	-	*Habis* (retentive or anti-secretory i.e. it works on the smooth muscles)	11
Celery (*Apium graveolens*)	Essential oil	sedative	35
Fennel (*Foenaculm 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 pardinal 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 regime.

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.

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