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Controlled Clinical Trial Effect of Noni Fruit Extract (*Morinda citrifolia*) Toward Overactive Bladder Women through Observation of High-Sensitivity C-reactive Protein in Urine Levels

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Abstract

BACKGROUND: The prevalence of overactive bladder (OAB) appears to increase with age (aging), and free radicals most contribute to an increase in the aging process. But now, some researchers have found the efficacy of *Morinda citrifolia* in inhibiting the oxidative stress process so that it is expected to be beneficial for the treatment of OAB.

AIM: The aim of this study was to find out the effect of *M. citrifolia* extract on overactive women bladder (OAB) through observation of high-sensitivity C-reactive protein (hs-CRP) urine level.

METHODS: This research is an experimental study using double-blind randomized controlled trial design conducted at General Hospital H. Adam Malik Medan, USU Pharmacy Laboratory for extraction of noni fruit (*M. citrifolia*) and the Integrated Laboratory of Biochemical-Biomolecular USU Faculty of Medicine for the examination of hs-CRP urine levels. A t-dependent test is performed if data distribution is normally distributed or if not normally distributed, the median values are compared with the Mann–Whitney U-test. The effect of noni in hs-CRP levels performed by wilcoxon signed-Ranks Test. The statistical significance test with CI 95% and significant difference value p<0,05.

RESULTS: These results indicate that the noni fruit extract has weak antioxidant activity (IC_{50} >150 ppm). From the statistical analysis, a significant difference ($p < 0.05$) was obtained in hs-CRP urine level after compared to before treatment. These results indicate that after treatment, there was an improvement in the degree of OAB symptom scores in Group A and Group B.

CONCLUSIONS: Noni fruit extract (*M. citrifolia*) is proven to be able to inhibit oxidative stress in urothelium through observation of hs-CRP urine levels in overactive women bladder (OAB).

Introduction

Overactive bladder (OAB) is one of the lower urinary tract syndrome with clinical symptom urgency, frequency, and nocturia, which is one of the condition cause health problem both in men and woman, especially in older people [1]. OAB clinical syndrome by overactivating detrusor muscle which it will over contracted the bladder. According to the International Continence Society, OAB is defined as clinical syndrome contains of urgency with or without incontinence and frequency, nocturia, with or without urinary infection or other pathology in the bladder. A systemic review by Milsom *et al*. showed that among 16.776 person frequency and urgency are the most clinical symptom found in patients (85% and 54%, respectively) [2].

Vignoli said, the prevalence of OAB is about 16% in all population men and women, but it was increasingly happened in woman with age older than 40 years old [3]. Noble shows increasing urge incontinence in woman over 44 years old 2–19% and man over than 64 years old 0.3–9%. OAB with incontinence in woman was 9.3% and OAB without incontinence 7.6% [4]. According to Chapple *et al*. [5]. OAB Prevalence about 20% worldwide in China about 23.9% in South Korea 22.1% and in Taiwan 19.7% which is more effected in woman than men and the prevalence getting higher in older people 27.9% >60 years old [6].

The risk factor that affects OAB is increasing age, differentiation of gender, obesity, lifestyle, socioeconomic, and history of pregnancy and operation. Increment in age causes OAB because there are degradating cells and molecular system of the vascular, dysfunction and hyper-permeability vascular and brain, increasing of stress oxidative, and inflammation [7].

Bladder inflammation is anticipated by sensory nerve neuroplasticity so that there are an increase in nerve growth factor (NGF) levels in the urine, thus acting as a biomarker in the pathogenesis of OAB [8]. Bladder inflammation also stimulates serum C-reactive protein (CRP) levels in OAB men and women and results in a

significant increase in serum CRP levels in patients with wet OAB (2.96 ± 0.47 vs. 0.93 ± 0.27 mg/L, $p < 0.01$) and dry OAB (2.96 ± 0.47 vs. 1.06 ± 0.16 mg/L, $p < 0.05$), as compared to normal individuals [9].

Bladder overactivity is more often in woman than men because the hormonal system in the neurotransmitter of hydroxytryptamine (5-HT) in the central nervous system leads to decreasing inhibition of micturition can cause OAB [10].

Obesity leads to OAB because increasing pressure of the abdomen increasing pressure of bladder cause urgency and frequency. Lifestyle factor alcoholic woman, tea, and coffee consumer will have a risk of OAB. Smoking is one of the risk factor of OAB. Incidences of LUTS in America, there are 27% Asian women, has OAB 43% in white people, 46% in African-American women, and 42% Latin America. A history of pregnancy woman which has previous spontaneous vaginal delivery predicted has OAB 4 times than normal woman [11].

Diagnostic procedure to OAB by history taking looking for symptoms of urgency, frequency, and nocturia. Laboratory test for urinalysis to detect urinary tract infection (UTI). Cystoscopy to exclude other blader abnormalities such as diverticulae, bladder stone, interstitial cystitis, urethral stricture, and obstruction of the bladder outlet. urodynamic procedure to assest detrusor overactivity [12].

Biomarker for OAB, one of theory of OAB is nerve inflammation that related to overexpression calcitonin gene-related peptide, substance P, brain derived neurotropic factor, NGF, CRP, prostaglandin (PG), adenosine triphosphate, and nitric oxide (NO) [13].

CRP is one the leading protein as an inflammation marker activites the ligand will increas opsonization. CRP trigger syntetic of interleukin (IL)-1, tumor necrosis factor-α (TNF-α), and IL-6 on mononuclear peripheral vascular. In some study relation CRP and OAB on Boston Area Community Health, there are increasing levels of CRP serum and increasing odds from OAB patient. Increasing CRP level 1.83 ± 2.30 mg/L, this data support hypothesis inflammation process in the bladder as pathogenesis in OAB [14].

Noni fruit (*Morinda citrifolia*) a plant which is grow in torpical zone such as Africa, South America, Caribia, Australia, New Zealand, Pacific islands, China, Mlaysia, Indonesia, and India. This plant has many advantages from its root, trunk, and also the fruit. Noni fruit is administered in the Indonesian formulary that has security proof, and the benefits have proven empirically. Srinivasan research antioxidant enzyme from noni fruit extract is superoxide dismutase 12.74 ± 0.27 U/g, catalase 73.08 ± 3.01 U/g, glutathione reductase 12.37 ± 0.33 U/g, glutathione peroxidase 36.94 ± 2.13 U/g and glutathione s-transferase 7.21 ± 0.17 U/g, ascorbic acid 23.6 ± 1.0 mg/g, α-tocopherol 83.5 ± 0.5 mg/g, carotenoids 3.347 ± 0.006 mg/g, and ferric reducing antioxidant power about 0.186 ± 0.0004 mg/mL that this data show that noni fruit has activity potential antioxidant [15].

Clinical Trials

This research was an experimental study using a double-blind randomized controlled trial design conducted at the H. Adam Malik General Hospital Medan, USU Pharmacy Laboratory, for extracting *M. citrifolia* and the Integrated Laboratory of Biochemistry-Biomolecular USU Faculty of Medicine for the examination of high-sensitivity CRP (hs-CRP) urine levels. This study was approved by the ethics committee Universitas Sumatera Utara regarding the implementation of health research no. 741/TGL/KEPK FK USU-RSUP HAM/2019.

The research sample was 56 female nursing health workers General Hospital. H. Adam Malik Medan who experienced OAB met the inclusion criteria that were willing to participate in the study and signed informed consent, women who were diagnosed with OAB based on OAB symptom scores (OABSS) and the results of urinalysis; and exclusion was consuming hormone replacement therapy, suffering from diabetes mellitus, suffering from UTIs, taking anti-depressant drugs, smoking, consuming alcohol, damaged samples, and withdrawing from research taken by the nonprobability method with consecutive sampling technique.

After obtaining approval from the Medical Faculty Ethics Committee University of North Sumatra and the Ethics Committee of RSUP H Adam Malik Medan, samples were taken at H Adam Malik General Hospital Medan. Sampling was done through interviews, filling out the OABSS questionnaire and urinalysis examination. The interview contained complaints of current illness, age, duration of menopause, and history of previous illnesses. Then, we measure womens height (m) and weight (kg) to determine of their body mass index. Urinalysis examination is then performed to rule out UTI. The urine that is taken is the middle portion of urine that is accommodated in a sterile urine pot. Then, the middle portion of urine was taken as much as 1 pot of urine for the examination of hs-CRP levels in the Integrated Laboratory of Biochemistry-Biomolecular USU Faculty of Medicine. Group A: A group was given 5 mg of solifenacin drug capsules, one capsule daily for 30 days; then, blood and urine samples are examined. Group B: The group was given noni fruit extract capsules (*M. citrifolia*) at a dose of 500 mg (8–16 mg/kg body weight), one capsule a day for 30 days; then, the urine sample was examined.

Noni fruit extract is made by percolation using 70% ethanol solvent and done in the pharmacology laboratory, faculty of pharmacy, Universitas Sumatera

Utara. A total of 8 kg of *M. citrifolia* powder was put into a closed vessel, soaked with 70% ethanol, left for 3 h, and protected from light, while occasionally stirring using a shaker. The results of the immersion are put into a percolator that has been pre-packaged, allowed to stand for 24 h. About 70% ethanol is supplied to the reservoir, add ethanol solution continuously until the color of ethanol is clear. All ethanol reservoirs are combined; then, the solution is concentrated so that a thick extract is obtained. Then, the thick extract was evaporated with a rotary evaporator at a temperature of 45–50°C, then dried with a freeze dryer to obtain a thick extract. Thick extracts were added with starch manihot and starch maydis in a ratio of 1:1 to the sample, homogeneous using mortars and then dried using an oven with a temperature of 60°C for 24 h.

Data are processed and analyzed by the computerized system with statistical software. Data characteristics of the study sample were analyzed using descriptive statistics. Univariate data were urine hs-CRP levels. Data normality test is done by Shapiro–Wilk test. To see the difference in average levels of urine hs-CRP, before and after administration of noni fruit extracts was done by t-dependent test if the data distribution was normally distributed or if the data distribution was not normally distributed, the median value was compared with the Mann–Whitney U-test.

To see the effect of noni on urinary CRP hs-CRP levels, the Wilcoxon Signed-Ranks Test was performed. Statistical significance test with CI 95% and a significant difference value p <0,05.

Results

In this study, patients did not experience significant side effects that no patients were dropped out.

Research subject characteristics

From Table 1 in Groups A and B of OAB sufferers, the majority of samples were aged 51–55 years, 39.29 7% and 42.86% were already 2 years old at menopause, that is, 39.29% and 42.8% and were in the obese category weight, that is, 57.14% and 42.86%.

Table 1: Subject characteristics

Characteristics	Group A (n = 28) (%)		Group B (n =2 8) (%)		p*
Age (n, %) (years)					
41–45	6	21.43	5	17.86	
46–50	11	39.29	11	39.29	0.826
51–55	11	39.29	12	42.86	
Menopause status (n, %)					
Not menopause	7	25.00	6	21.43	
Menopause	21	75.00	22	78.57	
Menopause (n, %) (years)					
1	4	14.29	3	10.71	
2	11	39.29	12	42.86	
3	3	10.71	4	14.29	0.901
4	3	10.71	2	7.14	
5	0	0.0	1	3.57	
Body mass index (n, %)					
Normoweight	0	0.0	4	14.30	
Overweight	12	42.86	12	42.86	0.116
Obese	16	57.14	12	42.86	

*<0,05

Urine hs-CRP and degree of OABSS before treatment

From Table 2, the urine hs-CRP levels in Group A are higher than those in Group B, where the hs-CRP level 8.69 ± 1.94 versus 8.30 ± 2.67 pq/mg was obtained. Based on statistical analysis, there were no significant differences in urine hs-CRP levels (p = 0.523) between Group A and Group B before treatment.

Table 2: hs-CRP levels in Groups A and B before treatment

Content/group	N	Mean	SD	Minimum	Maximum	p*
hs-CRP (mg/L)						
Grp. A	28	8.69	1.94	4.94	12.80	0.503
Grp. B	28	8.31	2.67	1.78	14.60	

*Mann–Whitney U-test.

Table 3 shows that the urine hs-CRP levels in severe OABSS are higher than moderate and mild OABSS, which is at urine hs-CRP levels obtained 9.16 ± 1.43 mg/L compared to 8.46 ± 2.30 mg/L and 8.39 ± 2.60 mg/L versus 9.16 ± 1.43 mg/L. These results indicate an increase in the degree of OABSS in line with an increase in hs-CRP.

Table 3: hs-CRP levels for OABSS before treatment (n = 56)

Level OABSS	hs-CRP (mg/L)
	Mean ± SD
Mild (≤ 5)	8.39 ± 2.60
Moderate (6 – 11)	8.46 ± 2.30
Severe (≥ 12)	9.16 ± 1.43

Furthermore, observing the distribution of hs-CRP levels in both groups, the Saphiro–Wilk test was carried out because the sample size was <50, the data were not normally distributed.

In Table 4, these results indicate no significant difference (p > 0.05) of urine hs-CRP to the degree of OABSS between Group A and Group B before treatment.

Table 4: Differences in hs-CRP levels on OABSS before treatment

OABSS	Group A (n = 28)	Group B (n = 28)	p*
Mild (≤ 5)	n = 10 (35.71%)	n = 9 (32.14%)	
hs-CRP (mg/L)	8.49 ± 2.36	8.27 ± 2.99	0.624
Moderate (6–11)	n = 16 (57.14%)	n = 16 (57.14%)	
hs-CRP (mg/L)	8.67 ± 1.79	8.26 ± 2.76	0.706
Severe (≥ 12)	n = 2 (7.14%)	n = 3 (10.71%)	
hs-CRP (mg/L)	9.88 ± 0.74	8.67 ± 1.72	0.564

*<0,05

hs-CRP urine after treatment

In Table 5, hs-CRP levels in urine in Group B are lower than in Group A, that is, hs-CRP levels were 4.47 ± 1.22 mg/L compared to 4.51 ± 1.54 mg/L.

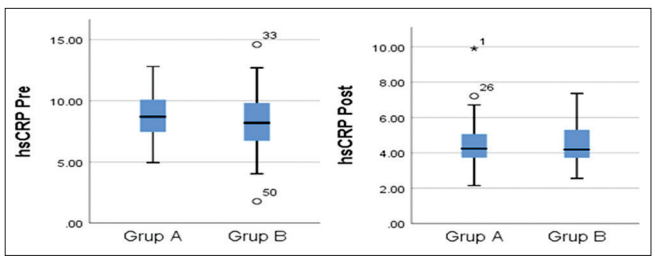

Figure 1: Differences in high-sensitivity C-reactive protein levels

In Figure 1, we can see there is a significant value of hs-CRP between solifenacin (group A) and noni fruit (group B), solifenacin more significant changes in pre and post test.

Table 5: hs-CRP levels after treatment

Kadar/Group	n	Mean	SD	Minimum	Maksimum	p*
hs-CRP (mg/L)						
Group A	28	4.51	1.54	2.15	9.89	0.993
Group B	28	4.47	1.22	2.56	7.36	

*Mann–Whitney U-test.

In Table 6, these results indicate no significant difference ($p > 0.05$) levels of hs-CRP in both mild and moderate OABSS between Group A and Group B after treatment.

Table 6: Differences in hs-CRP levels in OABSS after treatment

OABSS	Group A (n=28)	Group B (n=28)	p*
Mild (≥ 5)	n = 23 (82.14%)	n = 24 (85.71%)	
hs-CRP (mg/L)	4.33 ± 1.24	4.55 ± 1.24	0.663
Moderate (6–11)	n = 5 (17.86%)	n = 4 (14.29%)	
hs-CRP (mg/L)	5.35 ± 2.55	4.01 ± 1.19	0.327
Severe (≥ 12)	(n = 0)	(n = 0)	

*Mann–Whitney U-test.

The effect of M. citrifolia extract on hs-CRP OAB female urine

In Table 7, urine hs-CRP levels were lower after administration compared to before administration of solifenacin, which was 8.69 ± 1.94 pq/mg compared 4.51 ± 1.54 pq/mg. From statistical analysis, hs-CRP levels of urine were found to be $p < 0.001$, $p < 0.0001$, and $p < 0.0001$. These results indicate a significant difference ($p < 0.05$) in hs-CRP levels after administration compared to before administration of solifenacin.

Table 7: Effect of solifenacin and noni fruit extract on hs-CRP levels (n=28)

Content	Solifenacin		p*	*Morinda citrifolia*		p*
	Before	After		Before	After	
hs-CRP (mg/L)	8.69 ± 1.94	4.51 ± 1.54	<0.001	8.03 ± 2.66	4.47 ± 1.22	<0.0001

*Wilcoxon Test.

For the assessment of the effect of Noni extract versus solifenacin we can see the changes of hs-CRP levels of urine.

In table 8, we found that, the value of the effect of solifenacin is more significantly affect levels of hs-CRP urine than noni fruit extract (solfenacin effect size : 2,3, Noni fruit effect size : 1,72). From the data above, the value of the effect of solifenacin is more significantly affect levels of hs-CRP urine than noni fruit extract.

Table 8: Effect of noni fruit extract compared to solifenacin on changes in hs-CRP urine levels

Levels	Before	After	Effect size
hs-CRP (mg/L)			
Solifenacin	8.69 ± 1.94	4.51 ± 1.54	2,3
Noni fruit	8.03 ± 2.66	4.47 ± 1.22	1,72

The effect of M. citrifolia extract on female OAB

Table 9 shows that the majority of OABSS are in mild OABSS (85.71%), followed by moderate degree OABSS (14.29%). These results indicate that the administration of noni fruit extract has the same effect as giving solifenacin to a decrease in the degree of OAB in women.

Table 9: Differences in the effect of solifenacin and noni fruit extract on OABSS

OABSS	Solifenacin		Noni fruit	
	Before (n, %)	After (n, %)	Before (n, %)	After (n, %)
Mild (≤ 5)	10 (35.71)	23 (82.14)	9 (32.14)	24 (85.71)
Moderate (6–11)	16 (57.14)	5 (17.86)	16 (57.14)	4 (14.29)
Severe (≥ 12)	2 (7.14)	0 (0.00)	3 (10.74)	0 (0.00)

Discussion

Changes in neurotransmitters and increased inflammation and oxidative stress in the bladder contribute to OAB symptoms in the elderly population [16]. Bladder inflammation also stimulates serum CRP levels in OAB men and women [17]. Besides that, obtained mediators of inflammatory PGE2 which are synthesized in muscle and bladder mucosa will affect normal urinary reflexes and pathological conditions such as mucosal damage [18], as well as a significant increase in serum CRP levels in patients with OAB by 1 83 ± 2.30 mg/L. This data support the hypothesis of the bladder inflammation process in the pathophysiology of OAB [8].

Several questionnaire-based systems have been used to assess OAB and its treatment outcomes. Several scoring systems have been used, such as the OAB questionnaire, the patient perception of bladder condition, the primary OAB symptom questionnaire, OAB symptom composite score, urgency questionnaire, and OABSS. Chuang *et al*., in his study comparing several scoring systems to assess OAB patients, found that OABSS was not inferior to other questionnaires such as Urgency Severity Scale [19].

ROS is involved in the pathway that produces COX-2 expression in cells. The synthesis of PGs by cyclooxygenase (COX) depends on the peroxidase process. It is also known that lipoxygenase is activated by ROS. The first step in the arachidonic pathway is the release of arachidonic acid from the phospholipid membrane by the enzyme phospholipase A2. Arachidonic acid is then converted into eicosanoids through three pathways, namely, COX, lipoxygenase, and cytochrome P-450 (cyt P450). Antioxidants and enzymes are able to limit the process of peroxidation, thereby inhibiting the availability of COX-2. It is known that noni juice has an anti-inflammatory effect, with its capacity to be able to inhibit COX activity, which can inhibit COX-1 by 32% and COX-2 by 25%. In another study, a decrease in anti-inflammatory TNF-α and IFN-NO, NO, and IL-17 after administration of noni fruit juice [20]. Wang *et al*. had a significant reduction in hs-CRP by 15.2% ($p < 0.05$) others after taking TNJ 29.5 mL for 30 days [21].

Conclusion

Noni (*M. citrifolia*) extract is proven to inhibit oxidative stress in urothelium by observing levels of hs-CRP urine in OAB women.

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