



## Evaluation of Antihypertensive Effect of Shobhanjana and Patoladi Yoga in Uninephrectomy and DOCA Induced Hypertension in Wistar Rats

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**Abstract:** Hypertension is the most common chronic non communicable disorder. Most of the patients are asymptomatic and accidently diagnosed with hypertension. Long term raised BP (Blood pressure) results in various cardiovascular complications. Our aim is to evaluate the antihypertensive effect of Shobhanjana and Patoladi yoga in uninephrectomy and DOCA induced hypertension in wistar rats and to study its effect on biochemical parameters. Wistar rats of either sex weighing 200-250 gms were used for the study. Uni-nephrectomy was carried out under all aseptic precautions followed by daily ceftriaxone 200 mg/kg for five days. From the sixth day drinking water was replaced by 1% NaCl along with DOCA (Deoxycorticosterone acetate) subcutaneously in the dose of 20 mg/kg twice a week for four weeks. Hypertensive animals were randomly divided into five experimental groups. Test animals were given drug treatment orally and daily for 15 days, positive control group received Enalapril 10 mg/kg. Control and disease control group were treated with saline. Measurement of systolic, diastolic and mean BP was carried out on day 0, 7 and day 15. Blood collected for biochemical analysis on day 15. Significant decrease in systolic, diastolic & mean blood pressure was seen on day 7 & 15 with Shobhanjana ( $P < 0.01$ ) and Patoladi yoga ( $P < 0.01$ ) and Enalapril group ( $P < 0.01$ ) but combination (S+P) did not show synergistic effect. Patoladi yoga ( $P < 0.001$ ) was more effective than Shobhanjan ( $P < 0.05$ ) and Enalapril ( $P < 0.01$ ) in reducing cholesterol and Triglycerides. Shobhanjana and Patoladi yoga both showed anti-hypertensive activity comparable to Enalapril.

**Keywords:** anti-hypertensive, Uninephrectomy model, cholesterol, Triglycerides, Deoxycorticosterone acetate,

**Article History**      **Date of Receiving**      26 May 2020

**Date of Revision**      18 June 2020

**Date of Acceptance**      15 July 2020

**Date of Publishing**      20 July 2020

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**Funding** This Research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

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Int J Pharma Bio Sci., Volume 11., No 3 (July) 2020, pp P105-110



**Citation** Dawane JS, Khatavkar PS, Pandit VA and \*Mate VH, Evaluation of Antihypertensive Effect of Shobhanjana and Patoladi Yoga in Uninephrectomy and DOCA Induced Hypertension in Wistar Rats.(2020).Int J Pharm Sci.11(3), P105-110 <http://dx.doi.org/10.22376/ijpbs.2020.11.3.P105-110>

## I. INTRODUCTION

Hypertension is the most common chronic non communicable disease (NCDs) affecting worldwide, incidence of which is increasing at a very high rate. Non communicable diseases are more and more prevalent in developing countries.<sup>1</sup> NCDs are associated with genetic predisposition and multifactorial environmental influences related to lifestyle.<sup>2</sup> Metabolic changes that increases the risk of NCDs are raised blood pressure, obesity, hyperglycemia and hyperlipidaemia. Global deaths due to NCDs are attributed mainly to elevated blood pressure, followed by overweight, obesity and raised blood glucose. Blood pressure is the product of cardiac output and total peripheral resistance (TPR). Cardiac output is dependent on total blood volume, heart rate and the pumping action of the heart whereas peripheral resistance is determined by the diameter of arterioles. The Joint National Committee (JNC 8) (2014) and WHO-ISH guidelines (2003) have defined hypertension above 140 mm Hg systolic and 90 mm Hg diastolic.<sup>3</sup> Obesity, sleep apnoea, increased salt intake, excessive alcohol use, cigarette smoking, nonsteroidal anti-inflammatory (NSAID) therapy and low potassium intake are some of the predisposing factors for hypertension.<sup>4</sup> Most of the patients are asymptomatic and diagnosed accidentally. Therefore delay in treatment, lead to severe complications, such as hypertensive cardiovascular disease, hypertensive renal disease and atherosclerotic complications including stroke, coronary heart disease, renal insufficiency and heart failure. Therefore, Hypertension is labelled as an insidious "silent killer". Epidemiological studies have confirmed that higher the systolic and diastolic blood pressure, greater is the risk of cardiovascular disease.<sup>5</sup> Intensive lowering of blood pressure in hypertensive patients was associated with a low rate of cardiovascular events.<sup>6</sup> Lowering blood pressure also decreases albuminuria in type 2 diabetes and reduces the risk of nephropathy.<sup>7</sup> Shobhanjana (*Moringa oleifera*) plant is very important for its medicinal value. Various parts of this plant such as the leaves, roots, seed, bark, fruit, flowers and immature pods are studied for various activities like circulatory stimulants, antipyretic, antitumor, antidiuretic, anti-inflammatory,<sup>8</sup> antiepileptic, antiulcer, antispasmodic antihypertensive, cholesterol lowering, antidiabetic, antioxidant, antibacterial, hepatoprotective, and antifungal activities.<sup>9</sup> *Moringa oleifera* was also evaluated for antihypertensive effect and was found mild and brief antihypertensive.<sup>10,11</sup> The juice from the root bark is administered into ears to relieve earaches and also placed in a tooth cavity as a painkiller, and has anti-tubercular activity.<sup>12</sup> Patoladi yoga is the combination of Patola, Sariva, Musta, Patha and Kutki.<sup>13</sup> All of these are supposed to have blood purifying action. Individually, these agents are shown to have many actions like reducing hyperglycemia, anti-inflammatory, gastroprotective etc.<sup>14</sup> Shobhanjana and Patoladi yoga combination has shown to postpone the nephropathy in diabetic rats.<sup>15</sup> But there is paucity of authentic information regarding the utility of combination of these agents together in hypertension. Purpose of the study was to evaluate the

antihypertensive effect of Shobhanjana and Patoladi yoga in uni-nephrectomy and Deoxycorticosterone acetate (DOCA) induced hypertension in wistar rats.

## 2. MATERIALS AND METHODS

### 2.1 Animals

Experiments were carried out according to CPCSEA guidelines and approved by Institutional Animal Ethics Committee (IAEC) - BVDUMC/3021/2019/001/010 in adult albino wistar rats weighing 200-250g of either sex. Rats were maintained under standard housing conditions, room temperature 24–27° C and 12 h light and dark cycle. Food and water was available *ad libitum*.

### 2.2 Preparation of Extract:

Shobhanjana stem bark and Patoladi yoga obtained from authentic Ayurvedic shop. It was coarsely pulverised to fine powdered form. The aqueous extract of dried Shobhanjana stem bark and Patoladi yoga was prepared by addition of distilled water separately. About 10 grams of each powder were taken and mixed in 50 ml of distilled water. The mixture was taken into sterile conical flasks, plugged with sterile cotton and kept overnight and the solution was filtered through muslin cloth. These extracts were used for study.

### 2.3 Method to induce hypertension by DOCA salt

Surgical removal of kidney (Nephrectomy) -The skin above the dorsal aspect was shaved and disinfected. Under all aseptic precautions 1 cm incisions were made on the skin of the dorsal area left side. Skin separated, incision on muscle layer taken and separated with blunt artery forceps. The retractor was used to open the incision. Kidney identified and separated. One end of the surgical thread was tied to a pair of wide-tipped forceps and a single loop of thread was placed over the forceps tip. The kidney is pinched with the forceps. A second knot was made to secure the initial knot. The kidney was cut off above the surgical thread. The ureter and renal blood vessels were made to secure animal blood loss. Finally the two incisions were closed step by step. After completing the dressing, the rats were placed in a cage separately on a cotton bed and covered with cotton to minimize the heat lost. All operated rats received an injection of Ceftriaxone 200mg/kg daily for 5 days and local application of Povidone-iodine ointment to prevent infection after nephrectomy.<sup>16</sup> Postoperatively drinking water was replaced by 1% sodium chloride solution *ad libitum*. Deoxycorticosterone acetate dissolved in Olive oil and given at a dose of 20mg/kg subcutaneously twice a week for 4 weeks to the nephrectomies rats.<sup>17</sup> Blood pressure measurement was carried out to confirm the increase in systolic and diastolic blood pressure by using Non-invasive tail cuff method.<sup>18</sup> Animals were divided into following groups.

Groups of animals with drug treatment	
GROUP	Treatment given
1.Normal Control	Vehicle treatment
2.Disease Control	Vehicle treatment
3.Positive Control	Enalapril 10 mg/kg body weight
4.Shobhanjana	Shobhanjana 30 mg/kg
5.Patoladi Yoga	Patoladi Yoga 27 mg/Kg
6.Shobhanjana+ Patoladi Yoga	Shobhanjana 30 mg/kg+ Patoladi Yoga 27 mg/Kg

The animals of groups 4, 5, & 6 were administered test drugs as a single oral daily dose for 15 days, while positive control group animals were treated with the Enalapril 10mg/kg orally daily. [19] Animals of the control group were treated with saline. Blood collected at the end of the study by retro-orbital puncture for HB, LFT, BSL, and Cholesterol & Triglycerides

#### 2.4 Parameters assessed-

- Body weight
- Blood pressure -on day 0,7 & 15
- HB, LFT, BSL, Cholesterol & Triglycerides

Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were measured with non-invasive Rat Tail Cuff Blood Pressure System (MRBP, IITC Life Sciences Inc., USA) at baseline and on day 0, 7 and day 15 after starting treatment.<sup>20</sup> Before measurement, the animal was placed and relaxed in a rat holder at room temperature (25°C) about 15 to 20 min for acclimation. At least three readings were recorded during each measurement. The maximum and minimum values were discarded and the remaining values were calculated as the average.

### 3. STATISTICAL ANALYSIS

Statistical analysis was carried out using Graph pad Prism 6 software. Results were expressed as mean  $\pm$  standard error of the mean (SEM). The differences of continuous variables among various groups e.g. control and treated groups were tested using one-way analysis of variance (ANOVA), followed

by post-hoc Tukey's multiple comparisons tests. Statistical significance was assigned for *P*-values of less than 0.05.

## 4. RESULTS

### 4.1 Body weight

The body weights of rats were measured every week. At the beginning of the experiment, weights of rats were approximately similar in each group. Increase in body weight was observed in the control group at the end of the study. The rate of weight increase was reduced in the Nephrectomies animals, compared to that in the control group (Table.1) In disease control group it remained towards the lower side.

### 4.2 Blood Pressure

After 15 days treatment, hemodynamic parameters like systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were significantly higher ( $p < 0.001$ ) in the disease control group compared to the control group. Treatment with Enalapril 10 mg/kg significantly attenuated the increase in SBP, DBP and MAP. Systolic & Diastolic BP gradually decreased in all drug treated groups. BP lowering effect in S+P was significantly ( $p < 0.01$ ) lower than the disease control group but is equal to the effect of individual agents. Patoladi yoga appeared more effective than other drug treated groups though not significant. However, there was no significant change in heart rate between the groups. Animals of either sex were included in the study, but no significant difference was observed in reduction in blood pressure considering the sex of the animals.

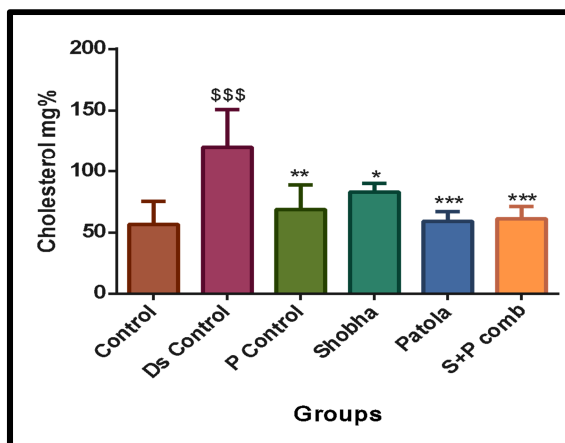
Groups	Control n=6	Ds-Control	Po-Control	Shobha	Patoladi yoga	S+P
BW (g)	221.6 $\pm$ 11	188.5 $\pm$ 18.1	211.83 $\pm$ 31	212.33 $\pm$ 5.8	212 $\pm$ 11.9	227.83 $\pm$ 20
SBP(mmHg)	117.5 $\pm$ 1.47	161 $\pm$ 3.27	146.33 $\pm$ 2.27**	147.83 $\pm$ 1.57**	146.16 $\pm$ 1.66**	146.16 $\pm$ 2.78**
DBP(mmHg)	82.33 $\pm$ 2.4	117.83 $\pm$ 2.98	97.83 $\pm$ 1.88**	97.16 $\pm$ 2.13**	96.0 $\pm$ 4.63**	95.83 $\pm$ 4.98**
MBP(mmHg)	93.83 $\pm$ 1.94	132.88 $\pm$ 1.68	113.99 $\pm$ 0.86	113.99 $\pm$ 1.63	112.57 $\pm$ 3.13	112.71 $\pm$ 3.74

Values expressed as mean $\pm$ SEM, SBP-systolic blood pressure, DBP- Diastolic blood pressure, MBP- Mean blood pressure, Ds-Disease, Po-Positive, Shobha-shobhanjan, S+P- shobhanjan+Patoladi yoga \*\* $P < 0.01$

### 4.3 Lipid Profile

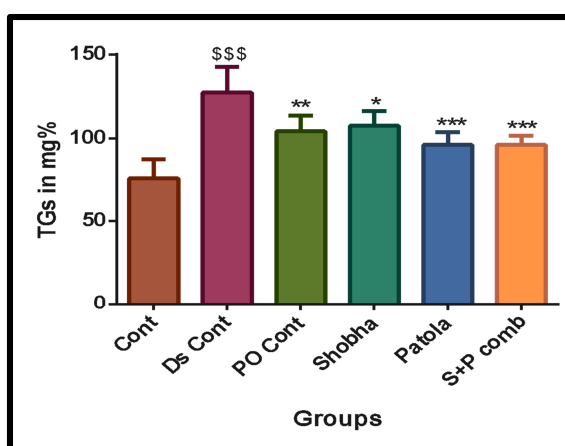
Increase in the cholesterol levels were observed in the disease control group compared to the control group. In Shobhanjana (*Moringa oleifera*) group significant reduction ( $p < 0.05$ ) was observed. Enalapril also showed significant reduction ( $p < 0.01$ ) in the cholesterol levels. Effect of

Shobhanjana was less than Enalapril. Patoladi yoga was more effective ( $p < 0.001$ ) in reducing cholesterol level in comparison to disease control animals, Shobhanjana and Enalapril treated rats. (Graph 1). Patoladi yoga was more effective than Enalapril, Shobhanjana and positive control animals. Similar patterns of results were seen on Triglyceride levels with both the drugs (Graph 2).



Values are expressed as Mean ± SEM; \$\$\$ P<0.001 in comparison with control; \*P<0.05, \*\*P<0.01, \*\*\*P<0.001 in comparison with disease control. Shobha-Shobhanjana, Patola-Patoladi yoga, S+P Combination of Shobhanjana & Patoladi yoga

Graph 1- Effect on Cholesterol levels



Values are expressed as Mean ± SEM; \$\$\$ P<0.001 in comparison with control; \*P<0.05, \*\*P<0.01, \*\*\*P<0.001 in comparison with disease control. Shobha-Shobhanjana, Patola-Patoladi yoga, S+P Combination of Shobhanjana & Patoladi yoga

Graph 2- Effect on Triglyceride levels

## 5. DISCUSSION

Hypertension is an important worldwide public health challenge. It is a major cause for morbidity and mortality.<sup>21</sup> In India Hypertension is responsible for 57% of stroke deaths and 24% of all coronary heart disease deaths.<sup>22</sup> WHO rates Hypertension also as one of the most important cause of the worldwide premature death.<sup>23</sup> Rat model of uninephrectomy followed by DOCA administration was used to test the antihypertensive activity of Shobhanjan and Patoladi yoga. Surgical removal of one kidney followed by administration of a synthetic mineralocorticoid derivative DOCA, along with salt loading in drinking water is a reliable model of hypertension with cardiovascular remodelling. Hypertension in this model is due to RAAS overactivity producing-Vasoconstriction & Aldosterone secretion, leading to increased sympathetic activity. The changes seen in humans after volume-overload induced hyper-tension, hypertrophy, fibrosis, conduction abnormalities and endothelial dysfunction can be studied in this model.<sup>24</sup> There is also an increase in vascular superoxide anion generation and altered endothelium dependent vascular relaxations.<sup>25</sup> Enalapril was used as a comparator, a prodrug, deesterified in the liver to enalaprilat, more potent, effective in reducing blood pressure. Due to longer duration of action, most

hypertensives can be treated with a single daily dose. Less adverse effects like rashes and loss of taste.<sup>26</sup> Shobhanjana leaves (*Moringa oleifera*) are vasodilator, anti-oxidant and also diuretic because of their high water content which helps to lower the blood pressure. Nitrile, mustard oil glycosides and thiocarbamate glycosides have been isolated from *Moringa* leaves, which were found to be responsible for the blood pressure lowering effect.<sup>27</sup> In our present study blood pressure lowering effect of stem bark of Shobhanjana was clearly observed on SBP, DBP & Mean BP. In our previous study on Shobhanjana and Patoladi yoga, it was observed that both the ingredients were effective in reducing BUN & creatinine and thus was effective in reducing diabetic nephrotoxicity. The effect of combination of Shobhanjana and Patoladi yoga was more significant and therefore in the present study the combination group was added to study the antihypertensive effect.<sup>28</sup> Vasodilation by reducing total peripheral resistance and venous return, diuretic action by reducing sodium and water overload and some additional mechanisms must be responsible for blood pressure lowering effect of stem bark aqueous extract of Shobhanjana. The crude extract of *Moringa* leaves has a significant cholesterol lowering action in the serum of high fat diet fed rats which might be attributed to the presence of a bioactive phytoconstituent, i.e. sitosterol.<sup>29</sup> Stem bark extract has

hypolipidemic and antioxidant effect and showed cardioprotective effect in isoproterenol induced cardiotoxicity.<sup>30</sup> In present study, marked cholesterol and triglyceride reducing effect was evident. Findings are consistent with previous reports of hypolipidemic action. Individual ingredients of Patoladi yoga, Patola, Sariva, Musta, Patha and Kutaki have been studied for antihypertensive and lipid lowering effects. Avhad et al. showed that Patoldi yoga was effective in lowering high blood pressure. All the symptoms like headache, anxiety, palpitation and insomnia showed significant improvements.<sup>31</sup> This compound has also showed effective reduction of cholesterol, triglyceride. Sariva and Kutaki possess the hypotensive activity.<sup>32</sup> Musta, Katuki and Patha have the smooth muscle relaxant action.<sup>33</sup> Diuretic action is also found in all these drugs. Due to all such properties the fall in high blood pressure was seen. Further, Musta has the tranquilizing action<sup>34</sup> and Patha possesses anxiolytic effect.<sup>35</sup> Though individual agents have been studied for the hypotensive effect and hypertension related symptoms, no study is available for the antihypertensive effect of Patoladi yoga. In the present study, it was observed that it is highly effective in reducing the SBP, DBP & Mean BP and also was found to be effective in reducing cholesterol and triglycerids. Both the drugs Shobhanjana and Patoladi yoga were equi-effective to Enalapril, indicating that both the drugs reduce RAAS over activity and show reduction in blood pressure. Hyperlipidemia is the major cause of atherosclerosis, which is an important risk factor of ischemic heart disease. Complications of hypertension are due to atheromatous vascular changes, where lipids- cholesterol and triglyceride play an important role. So, reduction of cholesterol and triglyceride is important for prevention of complications. Significant lipid lowering was the important additional activity encountered to Shobhanjana and Patoladi yoga. Interventions that reduce the concentrations of reactive free radicals such as superoxide, either by

decreasing production or increasing removal, decrease the remodelling in the DOCA-salt heart and vasculature.<sup>36</sup> Both these agents have antioxidant effects. The combination of blood pressure and lipid lowering along with diuretic constituents make these preparations highly useful in cardiovascular disorders.

## 6. CONCLUSION

Shobhanjana and Patoladi yoga both showed reduction in systolic and diastolic blood pressure, has anti-hypertensive activity. Antihypertensive activity was comparable to Enalapril. Treatment with both the drugs at the same time in combination did not provide any additional benefit. Shobhanjana and Patoladi yoga reduced cholesterol and triglycerides significantly. Patoladi yoga was more effective in lipid lowering effect. These agents showed promising effects on the uninephrectomy and DOCA induced hypertension in wistar rats. So they can be considered as the adjuvants in the treatment of hypertension. Further studies are required to study the detailed mechanism of action which is responsible for antihypertensive activity

## 7. AUTHORS CONTRIBUTION STATEMENT

Dr.Dawane and Dr.Pandit conceived the presented idea, developed the theory. Dr.Dawane and Dr.Khatavkar carried out the experiment and performed the computations. Dr.Mate and Dr.Dawane contributed in biochemical analysis and interpretation. All authors discussed the results and contributed to the final manuscript.

## 8. CONFLICT OF INTEREST

Conflict of interest declared none.

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