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A clinical study on Zaghatuddam Qawi Ibtidai (Essential Hypertension) and its management with Unani formulation, A Randomised controlled study

Dr. Asrar Ahmad Wani and Rais-ur-Rahman

Abstract
Essential Hypertension (Zaghatuddam Qawi Ibtidai) may be defined as sustained high blood pressure not attributable to a single cause but reflecting the interaction of multiple genetic and environmental influences. The term "Zaghatuddam Qawi" has not been mentioned in the classical Unani literature, however palpitation, vertigo & giddiness and heaviness in the head which are some of the symptoms of hypertension, are also seen as clinical features in a condition known as "Imtala" described in Unani classical literature. But merely on the basis of these clinical features, hypertension can't be equated with the term "Imtala".

Hypertension is the most prevalent cardiovascular disorder which doubles the risk of cardiovascular diseases, e.g., ischaemic heart disease (IHD), congestive heart failure (CHF), ischemic & hemorrhagic stroke, peripheral arterial disease and renal failure. In conventional system of medicine several classes of drugs are being used to manage essential hypertension and reduce its complications, but apart from being effective, most of these drugs have drastic side effects. In order to overcome the problem of essential hypertension and its management, a clinical study with a polyherbal Unani formulation containing 50% hydro-alcoholic extract of Sankha Holi (*Evolvulus alsinoids*), Asgandh (*Withania somnifera*), Parseavshan (*Adiantum capillus*) and Filfil Siyah (*Piper nigrum*) has been undertaken. At the end of the study the test drug was found efficacious and safe for the treatment of essential hypertension.

Keywords: Essential Hypertension, Zaghatuddam Qawi Ibtidai, Imtala, Hydro-alcoholic, Sankha Holi, Asgandh, Parseavshan, Filfil siyah

Introduction
Essential Hypertension (Zaghatuddam Qawi Ibtidai) may be defined as sustained high blood pressure not attributable to a single cause but reflecting the interaction of multiple genetic and environmental influences [1]. In about 95% cases of hypertension the cause is not apparent and these patients are said to have essential hypertension [2]. The important progress has been made in disentangling genetic, fetal and environmental factors that determine blood pressure level [3]. Researchers suspect that variations in genes involved in the regulation of renin-angiotensin-aldosterone system might impair blood pressure control and contribute to hypertension [4]. Low birth weight is associated with subsequent high blood pressure [5]. Environmental factors that influence blood pressure include age, sex, race, family size, occupation, salt intake, physical activity, stress and strain, smoking, alcohol intake, obesity etc. [6-19].

Modern Unani physicians and authors use the term Zaghatuddam Qawi to designate the hypertension. Zaghatuddam Qawi in present concept cannot be traced from the classics of Unani in toto, however the condition called "*Imtala*" has been widely discussed by all the Unani Hakeems in the history [20].

Imtala is manifested with headache, congested eyes, pulsatile arteries, puffiness of face, heaviness in head, restlessness, yawning, epistaxis, dark-colored turbid urine, lethargy, warm body, but only some of the symptoms stated above are present in hypertension [20].

On the other hand, many Unani physicians described Khafqan (palpitations), Sakta (apoplexy), Sadar-wa-Duwar (giddiness and vertigo) etc. in which "Imtala" is one of the causes in all the above conditions [20]. Palpitation, vertigo and giddiness have also been seen as symptoms of hypertension, whereas the epistaxis and apoplexy are the complications of hypertension, however the term "Imtala" cannot be equated with the hypertension on the basis of etiopathogenesis.

Systemic hypertension is the most prevalent cardiovascular disorder. It is an extremely common health problem in geriatric population afflicting approximately 65% of the population in the 65 to 75 years old age-group [21]. According to the WHO 2008 estimates, the prevalence of hypertension in Indians was 32.5% (33.2% in men and 31.7% in women) [22]. The adoption of the American College of Cardiology/American Heart Association guidelines in the United States is projected to raise the prevalence of hypertension to 45.6% in adults [23].

Hypertension is one of the leading causes of the global burden of disease. Approximately 7.6 million deaths (13–15% of the total) and 92 million disability-adjusted life years worldwide were attributable to high blood pressure in 2001. Hypertension doubles the risk of cardiovascular diseases, including coronary heart disease (CHD), congestive heart failure (CHF), ischemic and hemorrhagic strokes, renal failure and peripheral arterial diseases [24].

Most patients with hypertension have no specific symptoms referable to their blood pressure elevation. The nonspecific symptoms that may be related to elevated blood pressure include headache, dizziness, palpitation and easy fatigability [25].

Ninety-one percent (91%) of cases of heart failure are preceded by hypertension, and half of all patients who suffer a heart attack (and two-thirds of those who have a first-time stroke) have a blood pressure greater than 140/90 mmHg. During the 10-year period from 1991- 2001, the actual number of deaths due to hypertension rose to 53% [26].

To overcome the problem of essential hypertension and its morbidity and mortality, day by day several new drugs are being introduced in conventional system of medicine, but apart

from being effective, most of these drugs have drastic side effects and are not able to completely reduce the mortality and morbidity rates. So, there is a need to develop such drugs that can manage the hypertension as well as have least side effects.

With the growing importance of the problem of hypertension, a clinical trial with 50% hydro- alcoholic extract of Unani formulation containing Sankha Holi (*Evolvulus* alsinoids), Asgandh (Withania somnifera), Parseavshan (Adiantum capillus) and Filfil siyah (Piper nigrum) has been undertaken, so as to evolve an effective treatment of Essential hypertension that may reduce some of its risk factors and certainly without much side effects.

Materials and Methods

The present clinical trial entitled as "A clinical study on Zaghatuddam Qawi Ibtidai (Essential Hypertension) and its management with Unani formulation, a randomized controlled study" has been undertaken in the department of Moalijat, Ayurvedic and Unani Tibbia College and Hospital Karol Bagh, New Delhi. The patients were selected from this hospital for the assessment of the efficacy and safety of test drug. Before starting the trial, the research protocol was submitted for ethical clearance. The institutional ethics committee of A & U Tibbia College Karol Bagh New Delhi has approved the protocol for the study. Individually every patient of hypertension was thoroughly questioned for detailed history of the disease. Patients were clinically examined and required hematological and biochemical investigations were carried out. Clinical signs, symptoms, and investigations were recorded on the prescribed case record form, designed for the study under the direct supervision of supervisors.

Objectives of the study

To evaluate the efficacy and safety of the Unani formulation in the management of Zaghatuddam Qawi Ibtidai (Essential Hypertension).

To provide the safe, patient friendly and toxicity free alternative therapy for the patients of Zaghatuddam Qawi Ibtidai (Essential Hypertension).

Inclusion criteria

- Patients of grade 1 hypertension (130-139/80-89 mm Hg).
- Patients of 18-65 years of age.
- Patients of any sex.

Exclusion criteria

- Patients above the age of 65 years and below 18 years.
- Pregnant and lactating women.
- Patients taking any other drug for hypertension.
- Patients taking oral contraceptives.
- Patients suffering from any other cardiovascular diseases, kidney disorders, thyroid disorders, CNS disorders, metabolic disorders such as obesity (BMI>30).

Patients suffering from secondary hypertension.

Study design

The study was designed as a randomized standard controlled clinical study.

Randomization

Sixty patients were randomly allocated by using lottery method into two groups, comprising 30 patients in each of test group and control group respectively.

Sample size

Sample size was fixed as 60 patients.

Duration of protocol therapy

The treatment period in both test and control groups was fixed as 42 days.

Dosage schedule

The study group received test drug in the dose of 2 capsules (500 mg each) orally twice daily with plain water for 42 days.

The control drug amlodipine (Amcard-5) one tablet of 5 mg was administered orally once daily with plain water for 42 days to the patients of control group.

Justification for selecting the Unani formulation

As evident from the drug management of this disease, it requires Musakkinat (tranquilizers), Munawwimat (hypnotics) to relieve sympathetic overactivity; Mudirrat-e-boul (diuretics) to excrete out excessive fluid and salt from the body; Musaffiyat and Moaddilat-e-dum (blood purifiers) to purify the blood and regulate the blood lipid level and Mufattihat-e-urooq-e- damvia (vasodilators) to decrease the peripheral resistance. This Unani formulation which is found to have all the requisite qualities like diuretic, sedative, vasodilatory, hypolipidemic and antioxidant properties that is why this particular formulation is selected for the proposed clinical trial.

Method of preparation of study drugs
The 50% hydroalcoholic extraction of the Sankha Holi (*Evolvulus alsinoids*), Asgandh (*Withania somnifera*), Parseavshan (*Adiantum capillus*) and Filfil Siyah (*Piper nigrum)* was carried out separately in the phytochemistry Research laboratory, Jamia Hamdard, New Delhi. Each of the above extracts was then packaged into capsules in the proportion as mentioned under; Each capsule contains Sankha Holi (*Evolvulus alsinoids)* extract 175 mg, Asgandh (*Withania somnifera)* extract 150 mg, Parseavshan (*Adiantum capillus)* extract 150 mg and Filfil siyah (*Piper nigrum)* extract 25 mg making total of 500 mg /capsule.
The control drug Amlodipine 5 mg (Tablet Amcard 5) was procured from the market.

Study procedure
Screening of the patients was done one week prior to the onset of the study. During the screening procedure the volunteers were properly interrogated, thoroughly examined physically, investigated and diagnosed. The BP of the patients was taken at 3 consecutive visits during physical and mental rest for making the diagnosis of Hypertension.

Informed consent
Patients fulfilling the inclusion criteria mentioned above were informed and they were made understand all about the study, investigations to be carried out, the drug to be used, method of treatment and were further asked to sign the informed consent form.

Parameters for the evaluation of efficacy of trial drugs in the treatment
To assess the response of treatment, the following subjective and objective parameters were used in the study.

Subjective parameters
Headache, Palpitation, Dizziness and Blurring.

An arbitrary grading of the above symptoms was made as under for feasibility of assessment of each symptom.

No Symptom 0
Mild Symptom 1

These symptoms are not severe enough to require remedial therapy to continue day to day activities.

Moderate Symptom 2

They do not interfere in day to day activities and require remedial therapy to continue routine work.

Severe Symptom 3

They do not allow to carry out daily activities in spite of taking required drug.

Objective parameters
Recording of blood pressure: Systolic and Diastolic blood pressures were recorded at the base line and later on at weekly intervals.

Investigations
The laboratory investigations such as haemogram, liver function test, kidney function test, lipid profile, blood sugar fasting and post prandial were carried out at base line, 10th day and 42nd day for assessment of efficacy and safety of the test drugs.

Assessment of temperament (Mizaj)
Determination of Mizaj (temperament) was done on the basis of ten classical parameters (Ajnas-e-Ashra) as prescribed in classical Unani literature.

Assessment of Mizaj (Temprament)

Parameters	Damwi (Sanguine)	Balghami (Phlegmatic)	Safravi (Bilious)	Saudavi (Melancholic)
Complexion	Reddy (Reddish)	Chalky (Whitish)	Pale (Yellowish)	Purple (Blakish)
Built	Muscular & broad	Fatty & broad	Muscular & thin	Skeletal
Touch	Hot & Soft	Cold & Soft	Hot & Dry	Cold & Dry
Hair	Black, lusty & thick, rapid growth	Black & thin, slow growth	Brown & thin, rapid growth	Brown & thin Slow growth
Movement	Active	Dull	Hyper active	Less active
Diet (Suitable)	Cold & dry	Hot & dry	Cold & moist	Hot & moist
Weather (Suitable)	Spring	Summer	Winter	Autumn
Sleep	Normal	In excess	Inadequate	Insomnia
Pulse	Normal 70-80/ minute	Slow 60-70/minute	Rapid 80-100/minute	Slow 60-70/minute
Emotions	Normal	Calm & quite	Angry	Nervous

Adverse / Side effects
Adverse / side effects if any were noted during the entire period of clinical study.

Statistical analysis
After six weeks of the treatment, the pre-treatment and post-treatment values of subjective and objective parameters of each group were analyzed statistically to evaluate the efficacy of the treatment by applying appropriate statistical tests.

Concomitant medication
All the Patients were advised that neither they should participate in any other study concomitantly nor to take any other drug without informing the investigator.

Observations and results
Effects of the trial drugs were observed in both the groups which are as under.

Effect of trial drugs on Systolic blood pressure
In the test group the mean systolic blood pressure was

reduced from 133.9 mmHg to 124.33 mmHg. The effect of the drug was found highly significant (t = 21.72, p = 0.0001). There was 7.14% improvement in systolic blood pressure.

In the control group the mean systolic blood pressure was reduced from 135.63 mmHg to

126.93 mmHg. The effect of the drug was found highly significant (t = 24.16, p = 0.0001). There was 6.14% improvement in systolic blood pressure.

Effect of trial drugs on Diastolic blood pressure

In the test group the mean diastolic blood pressure was decreased from 87.46 mmHg to 79.33 mmHg, the effect of the drug was found highly significant (t = 25.5, p = 0.0001). There was 9.29% improvement in diastolic blood pressure.

In the control group the mean diastolic blood pressure was dropped from 87.06 mmHg to

79.46 mmHg. The effect of the drug was found highly significant (t = 10.57, p = 0.001). There was 8.72% improvement in diastolic blood pressure.

Table 1: Intergroup comparison of test group vs control group on blood pressure

Blood Pressure		Mean (SEM) mmHg 0 Day	Mean (SEM) mmHg 42nd Day	% Change	t Value	P Value	Statistical Result
Systolic Blood Pressure	Test Drug	133.9 ± 1.01	124.33 ± 0.94	7.14%	21.72	0.0001	Extremely Significant
	Control Drug	135.63 ± 0.74	126.93 ± 0.71	6.41%	24.16	0.0001	Extremely Significant
Diastolic Blood Pressure	Test Drug	87.46 ± 0.27	79.33 ± 0.32	9.29%	25.5	0.0001	Extremely Significant
	Control Drug	87.06 ± 0.45	79.46 ± 0.43	8.72%	10.57	0.001	Very Significant

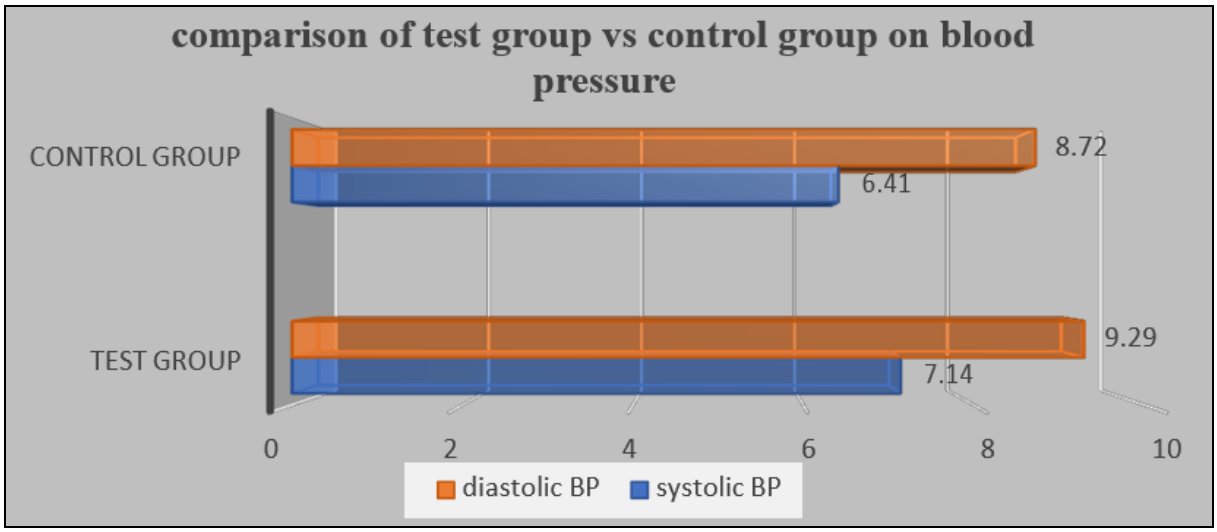

Fig 1: Comparison of test group vs control group of blood pressure

Effect of trial drugs on blood lipids

In the test group, mean serum cholesterol level was significantly reduced from 200.66 mg to

179.73 mg. The mean serum triglyceride level was significantly reduced from 172.4mg to 147.3mg. The mean serum low-density lipoprotein was significantly reduced from 123.37mg to 111.76mg and the mean serum very low-density lipoprotein was significantly reduced from 31.39mg to 27.54mg.

Effect of trial drugs on blood sugar

In test group, the mean fasting blood sugar level was significantly reduced from 97.2mg to 92.1mg and the mean post prandial blood sugar level was significantly reduced from 121.73mg to 109.6mg.

Effect of trial drugs on clinical features

In the test group, headache decreased by 100%, palpitation by 95%, dizziness by 100% and blurring of vision by 100%, while in the control group, headache was decreased by 94%, palpitation by 92%, dizziness by 100% and blurring of vision by 100%.

Table 2: Effect of trial drug on symptoms of test group

F/U in days	Before Treatment						After Treatment						
	0 days	7th Day		14th Day		21st Day		28th Day		35th Day		42nd Day	
Features	Total number of patients	Number of patients	Improved % age	Number of patients	Improved % age	Number of patients	Improved % age	Number of patients	Improved % age	Number of patients	Improved % age	Number of patients	Improved % age
Headache	18	17	5.5%	7	61%	3	83%	3	83%	1	95%	0	100%
Dizziness	8	5	37%	1	87%	1	87%	1	87%	1	87%	0	100%
Blurring of vision	3	2	33%	0	100%	0	100%	0	100%	0	100%	0	100%
Palpitation	22	18	18%	10	55%	3	86%	2	91%	2	91%	1	95%

Table 3: Effect of trial drug on symptoms of control group

F/U in Days Features	Before Treatment	After Treatment											
	0 days Total number of patients	7th day		14th day		21st day		28th day		35th day		42nd day	
Headache	17	11	35%	6	65%	4	76%	2	88%	1	94%	1	94%
Dizziness Blurring	7	4	43%	2	71%	0	100%	0	100%	0	100%	0	100%
of vision	2	1	50%	0	100%	0	100%	0	100%	0	100%	0	100%
Palpitation	25	23	8%	18	28%	6	76%	4	84%	2	92%	2	92%

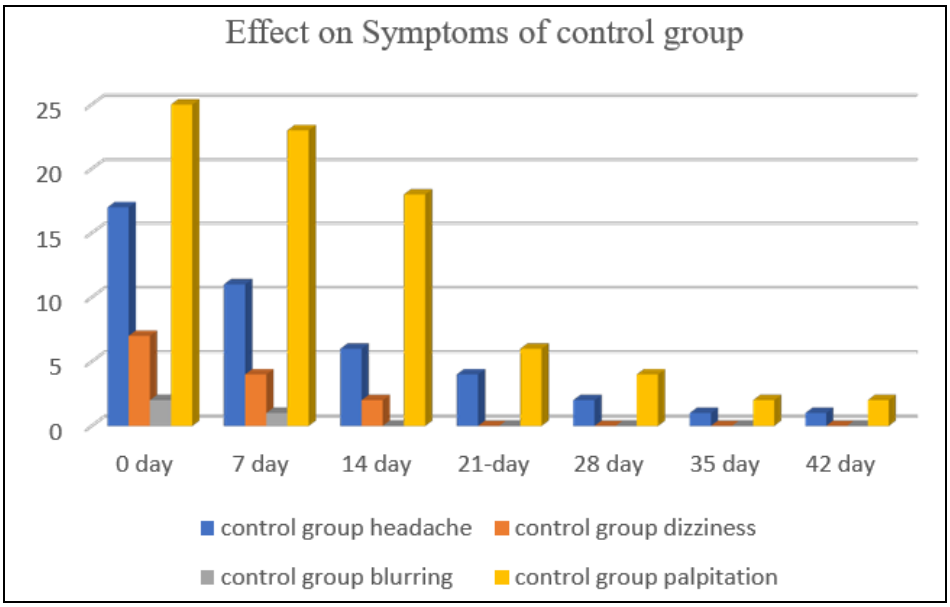

Fig 2: Effect on symptoms of control group

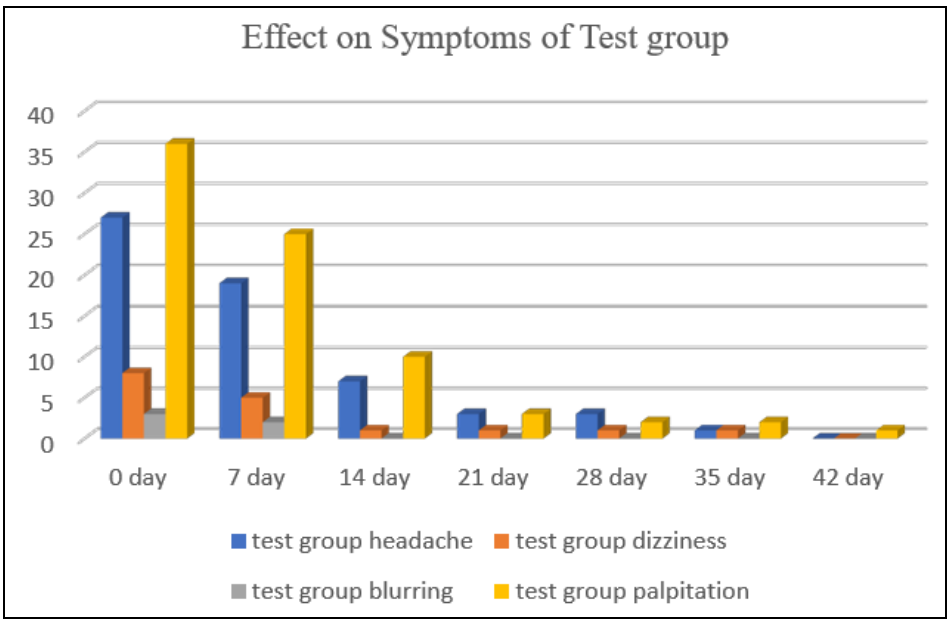

Fig 3: Effect on symptoms of test group

Safety Parameters

In this study safety parameters viz. Hemogram, Liver function test and Kidney function test were also assessed at baseline, 10th day and after the protocol therapy was over. On statistical analysis of the data no considerable difference was observed in both the groups. During the entire period of study, no adverse / side effects were reported.

Table 4: Safety assessment for test group (n=30)

Parameters		Assessments (Mean)		
		0 Day	10th Day	42nd Day
Haemoglobin		13.36	13.03	12.74
Total leucocyte count		7473.3	7153.3	6836.6
DLC	Polymorphs	60.8	61.2	60.3
	Lymphocytes	35.46	35.1	35.1
	Eosinophils	3.73	3.7	4.2
	Basophils	0	0	0
	Monocytes	0	0	0
LFT	Bilirubin	0.53	0.52	0.46
	SGOT	31.7	28.06	23.9
	SGPT	45.3	38.46	33.16
	Alkaline phosphatase	148.6	159.06	141.23
KFT	Blood Urea	23.83	21.4	20.53
	Serum Creatinine	0.84	0.8	0.73

Table 5: Safety assessment for Control group (n=30)

Parameters		Assessments (Mean)		
		0 Day	10th Day	42nd Day
Haemoglobin		13.48	12.93	12.48
Total leucocyte count		7776.6	7583.3	7456.6
DLC	Polymorphs	62.66	64.06	64.46
	Lymphocytes	33.86	32.93	32.83
	Eosinophils	3.63	2.8	3.1
	Basophils	0	0	0
	Monocytes	0	0	0
LFT	Bilirubin	0.65	0.64	0.61
	SGOT	31.96	28.16	28.53
	SGPT	37.36	33.93	29.96
	Alkaline Phosphatase	142.56	148.26	143.73
KFT	Blood Urea	24.8	23.7	24.43
	Serum Creatinine	0.84	0.83	0.83

Discussion

As we know Essential hypertension is a multifactorial disease involving genetic and environmental factors. In our study a positive family history of hypertension was found in 28 (46.66%) patients. Family studies have shown that probability to develop hypertension increases by 50% if both parents are hypertensive and it is evident in this study.

There were more house-wives than business class and service class in this study. Anxiety and stress act as a risk factor for essential hypertension. House-wives do suffer from life stresses more than any other class and are more often victims of discrimination, becoming vulnerable to anxiety, that is obvious from this study.

Majority of the patients in this study belonged to non-vegetarian class who consume large quantities of saturated fat containing food stuffs. Recent evidences suggested that the saturated fat increases blood pressure. High fat intake (Dietary fat representing 40% or more of the energy supply and containing a high proportion of saturated fats) has been identified as a major risk factor for essential hypertension.

In our study 14 (23.34%) patients and 4 (6.66%) patients were smokers and tobacco chewers respectively. There is evidence that smoking is an independent risk factor of hypertension as well as additional with other risk factors such as family history of hypertension, physical inactivity, added salt intake, saturated fat intake, mental stress etc.

The trial drug sub-sides the clinical features of hypertension significantly. During the course of the study, with the improvement in clinical features, we focused to record adverse effects of the drug at subsequent visits but there were no significant adverse effects of the drug. All of the patients showed good tolerability to the trial drug.

In this study, at the end of the 42nd day of the treatment, the systolic and diastolic blood pressures were reduced significantly from 133.9 mmHg to 124.33 mmHg and 87.46 mmHg to

79.33 mmHg respectively in the test group. The quality of the life of every patient of test group has improved at the end of the study. This highly significant result may be most likely because of the specific quality of the single ingredient of the trial drug as mentioned above.

Laboratory profile suggests that during the trial, lipid profile, blood sugar levels, kidney function test in the test group improved significantly. It indicates that, Unani formulation not only decreased the blood pressure significantly but also reduced the risk factors of essential hypertension. Besides this, no adverse / side effects were observed during the course of the study, rather the drug has been found absolutely safe and efficacious.

Probable mode of action of the Unani formulation

Evolvulus alsinoids contains many of therapeutic phytochemical constituents such as glycosides, alkaloids, flavonoids, tannins, resins and saponins. The antihypertensive effect of extract of whole herb was due to ACE inhibitor mechanism, as the extract lowered the blood pressure as similar to enalapril without interfering with pulse rate [50].

The evolvosids C–E, flavonol-4'-O-triglycosides, present in Evolvulus alsinoids have revealed significant anti-stress activity [51].

The alkaloids present in Withania somnifera have a prolonged hypotensive, brady-cardiac, and respiratory-stimulant actions. The hypotensive effect was mainly due to autonomic ganglion blocking action and that a depressant action on the higher cerebral centers also contributed to the hypotension [52].

Withania somnifera Glycowithanolides (WSG) possesses a potent anti-stressor effect by regulating sympatho-adrenal and hypothalamo-pituitary-adrenal (HPA) axis, reduces brain levels of tribulin, an endocoid marker of clinical anxiety, and reduces the sensitivity of the heart to adrenergic stimulation and thereby protects the heart against sympathetic outbursts [38, 41, 57].

Withania somnifera root extract also causes relaxant and

antispasmodic effects against various agents that produce smooth muscle contractions in intestinal, uterine, tracheal, and vascular muscles [39].

The parseavshan (*Adiantum capillus-veneris)* water extract is a good diuretic when used in a low dosage [45]. The aqueous and methanol extracts of parseavshan showed improvement in the fasting blood sugar [43]. Phytochemicals derived from water extract of Parseavshan (*Adiantum capillus-veneris*) may inhibit HMG-CoA reductase, thus advocating Phyto therapeutic strategy in atherosclerosis-related hypercholesterolemia, and the mode of action is similar to statins [44]. The essential oil obtained from Adiantum capillus veneris have high amount of carvone, carvacrol and thymol which is responsible for free radicals scavenging activity [42].

Piperine derived from Filfil siyah (*Piper nigrum*) showed antihypertensive effect mediated through calcium channel blockade [47, 48, 53, 54].

Piperine has been documented to enhance the bioavailability of a number of therapeutic drugs as well as phytochemicals thereby enhancing their efficacy [49].

By virtue of these properties, the selected Unani formulation showed a significant hypotensive effect besides having anxiolytic, antioxidant, hypoglycemic and hypolipidemic effects without producing any side effects in the test group. It also relieved the clinical features of hypertension better than Amlodipine.

In this study, there was no significant alteration in Hemogram, LFT and KFT at the end of study. During the entire course of the trial, no adverse drug reactions were reported by the patients or observed by the investigator. Thus, Unani formulation, appears to be highly effective and safe medication in the management of essential hypertension.

Conclusion

Amlodipine showed significant hypotensive effect and improved the clinical symptoms of essential hypertension without producing side effects. On the other hand, Unani formulation was found more effective in reducing the blood pressure and atherogenic lipid fraction, i.e. total cholesterol and serum triglycerides, in addition to significant decrease in blood sugar fasting and post prandial is due to effective drug combination. It also improved clinical features better than control drug, in addition anxiolytic, antioxidant, hypoglycemic and hypolipidemic activities were also found that were not found in control drug, which makes this formulation more ideal and specific for the treatment of essential hypertension. This underlines the importance of an effective antihypertensive treatment to prevent cardiovascular complications associated with hypertension.

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