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Comparative Clinical Study to Evaluate the Efficacy of an Herbal Drug with Thyroxine in the Management of Primary Hypothyroidism

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ABSTRACT

Background: Hypothyroidism was the first endocrine disorder to be treated with replacement of the deficient hormone. Initially animal glandular extracts were used. Synthetic LT_4 is widely available today, as its Na salt in multiple strengths between 25 ug and 200 ug, and is the therapy of choice. The absorption is 80% in fasting state decreasing to 60% in the fed state. Desiccated thyroid, an animal preparation containing T_3 and T_4 in a ratio of 1:11 is still available but rarely used. A combination of T_3 and T_4, 12.5 ug of T_3 and T_4 is available and may be useful in minority of patients. Traditionally, the tablet is given in the morning. The half-life of serum T_4 is 7 days which allows a single daily dosing.[1-5]The goal of treatment of hypothyroidism is the restoration of an euthyroid state in all tissues. This is usually achieved in patients with primary hypothyroidism by restoration of serum TSH concentrations to normal. The average full replacement dose is 1.6 ug/kg/d with inter-individual variation. Requirements for infants and children are higher.[2,6] Though hormone replacement therapy has proved effective in the management of Hypothyroidism, but owing to adverse effects on long term use, the need to search for effective herbal drugs from the treasures of *Unani* system of Medicine(USM) for the management of Hypothyroidism was felt by the Researchers of the field and a herbal drug ***Commiphora mukul (Muqil)***[23-27] which has shown positive thyroid activities in experimental animals was selected to check its comparative efficacy with thyroxine. Hence a clinical study titled 'comparative clinical study to evaluate the efficacy of an herbal drug with thyroxine in the management of primary hypothyroidism was designed.

Key words: Hypothyroidism, TSH, Thyroxine, Hormone, Herbal drug.

INTRODUCTION

Hypothyroidism was the first endocrine disorder to be treated with replacement of the deficient hormone. Initially animal glandular extracts were used. Synthetic LT_4 is widely available today, as its Na salt in multiple strengths between 25 ug and 200 ug, and is the therapy of choice. The absorption is 80% in fasting state decreasing to 60% in the fed state. Desiccated thyroid, an animal preparation containing T_3 and T_4 in a ratio of 1:11 is still available but rarely used. A combination of T_3 and T_4, 12.5 ug of T_3 and T_4 is available and may be useful in minority of patients. Traditionally the tablet is given in the morning. The half-life of serum T_4 is 7 days which allows a single daily dosing.[1-5]The goal of treatment of hypothyroidism is the restoration of an euthyroid state in all tissues. This is usually achieved in patients with primary hypothyroidism by restoration of serum TSH concentrations to normal. Hypothyroidism can affect all organ

systems, and these manifestations are largely interdependent of the underlying disorder but are a function of the degree of hormone deficiency. The clinical features include somnolence, fatigue, weight gain, cold intolerance, loss of appetite, constipation, hoarseness of voice, loss of libido, menorrhagia, polymenorrhea, dyslipidaemia, polyarthralgias, myalgias, decreased reflexes etc.[7-22.]

Even though hormone replacement therapy (HRT) with Thyroxine has proved effective in the management of Hypothyroidism, but owing to adverse effects on its long term use, the need for search of a safe herbal drug from the treasures of Unani system of Medicine (USM) was deeply felt. Hence a clinical study titled 'comparative clinical study to evaluate the efficacy of an herbal drug with thyroxine in the management of primary hypothyroidism' was designed to compare the efficacy of *Commiphora mukul (Muqil)*[23-27]with Tab. Thyroxine in Hypothyroid patients.

METHODS

Eligibility criteria

Inclusion criteria: Clinically diagnosed Male, female patients in the age group of 20-60 years with Primary Hypothyroidism**,** who showed Willingness to sign the informed consent, follow the protocol and participate in clinical trial voluntarily.

Exclusion criteria

Patients below 20 and above 60 years, Patients on iodine containing vitamins or minerals, Patients who have undergone thyroid surgery, taken radioactive iodine therapy, Renal dysfunction, Patients who fail to give consent, patients with diabetes mellitus, liver disorders, GIT diseases, pregnant and lactating mothers and all complicated cases of hypothyroidism.

Selection of cases

The source for selection of cases was the Out-patient department of Regional Research Institute of Unani Medicine (RRIUM) Srinagar. History, clinical examination and laboratory investigations were the basis for enrolling patients for the study. Ethical approval was provided by the Institutional Ethical Committee of RRIUM Srinagar.

Investigations

A set of investigations were carried out in all the patients to include or exclude from the study and to assess the efficacy and effect of test and control drug on different parameters which included:

Complete blood counts (CBC)
Erythrocyte sedimentation rate (ESR)
Fasting Blood sugar (FBS)
Lipid profile
Liver function test (LFT)
Kidney function test (KFT)
Urine examination
E.C.G.
Thyroid function test (TSH,T4 ,T_3)

All the above-mentioned investigations were carried out in all the before the commencement of the study and after the completion of the study.

METHODOLOGY

All the patients were advised to discontinue any drug they might be taking for the management of hypothyroidism to assess the unbiased effect of therapies. The drug was withdrawn 1 week before including the patient in the clinical trial.

Consent of the patient

Before enrolling the patients for the study, every patient was provided a set of specially designed Information Consent Form (ICF) which included all the relevant information about the study, investigations , drug, method of treatment and follow-up plan with all the options to ask any query regarding the study. After that when he/she signed the Information Consent Form (ICF), the treatment was started.

Study design

A randomized, single blind, standard controlled clinical study

Sample size

A sample size of 60 patients with 30 in test and 30 in control group

Allocation of group

Lottery method of randomization was used for allocation of group with Group A as Test group and Group B as control group with 30 patients in each group.

Drugs and dosage

The test drug *Commiphora mukul (Muqil)* was given in a dose of1 gm twice daily orally with lukewarm water after meals and the control drug Tab. Thyroxine 50 mcg orally in the morning once daily.

The trial drug was procured from Market from reputed suppliers after duly identified by experts which was then processed in the Pharmacy Deptt of a Unani College in Srinagar, and the control drug was purchased from the market.

Duration of study

The duration of study was 60 days in both the test and control groups.

Follow-up plan for patients

Follow up was done on 15th day, 30th day, 45th day, 60th day in both the groups. On every follow up, patients were assessed for improvement of their symptoms or worsening of symptoms, appearance of any new symptom, adverse drug effects if any. All the clinical parameters were checked and were recorded in Case Record Form (CRF).

Assessment of Efficacy/Result

The subjects in both test and control groups were assessed for subjective and objective parameters. Subjective parameters included Somnolence, Fatigue, Puffiness of face, Hoarseness of voice, dry skin, decreased libido, delayed tendon reflexes and non-pitting edema while as objective parameters included TFT, Lipid profile etc. The clinical symptoms and signs were found to be different from patient to patient and therefore grading of subjective parameters was done arbitrary for assessment and evaluation of symptoms and efficacy of the test drug as well as control drug. Before the commencement of treatment, each subjective parameter was recorded in graded form in case record form depending upon the severity of symptoms from 0-3 with 0 for no symptoms,1-mild,2-moderate and 3-severe.

Grade-0	Absent
Grade-1	Mild
Grade-3	Moderate
Grade-4	Severe

Safety Assessment

All the patients enrolled for the study were assessed for safety pre and post treatment protocol on following parameters:

a. Clinical check-up at every follow-up.
b. Complete Blood Picture like CBC, ESR, & Urine exam on pre (Day 0) and post treatment (Day 61) after completion of the treatment protocol.
c. Blood sugar fasting, LFT, KFT, ECG were done before (Day 0) and after treatment (Day 61).

OBSERVATIONS AND RESULTS

Table.1: Showing Age Distribution among Test group and Control group (n=60)

Age(years)	Test group		Control		P value
	No	%age	No	%age	0.5
20-30	7	23.3	2	6.7	
31-40	6	20.0	10	33.3	
41-50	10	33.3	10	33.3	
51-60	7	23.3	8	26.7	
Total	**30**	**100.0**	**30**	**110.0**	
Mean±SD	**38.47±11.25**		**40.23±9.91**		

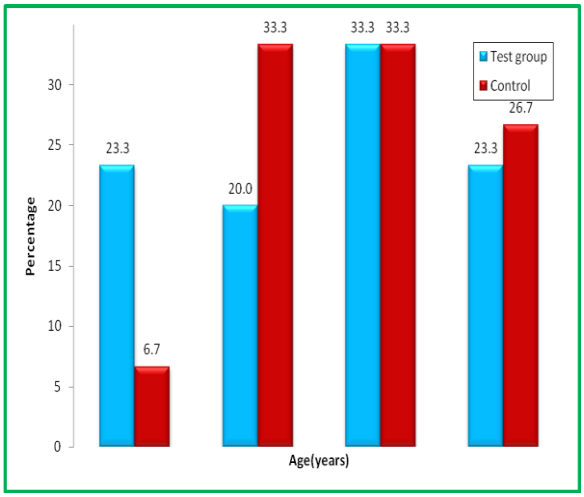

Figure1: Showing Age Distribution among Test and Control groups (n=60)

The maximum number of patients were found in the age group 41-50 years

(33.3%), followed by 20-30 years (23.3%), 51-60 years (23.3%), 20-30 years (6%) in test group and 31-40 years 33.3%, followed by 41-50 years (33.3%),51-60 years (26.7%), 20-30 years (6.7%) in control group.

Table 2*: Showing Sex Distribution among Test group and Control group (n=60)

SEX	Test group		Conrol		P value
	No	%age	No	%age	
Male	7	23.3	6	20.0	0.75
Female	23	76.7	24	80.0	
Total	**30**	**100**	**30**	**100**	
Test applied: Fisher's exact test					

Out of 60 patients, 76.7 % were females and 23.3% were males in Test group and 80% were females and only 20% were males in Control group.

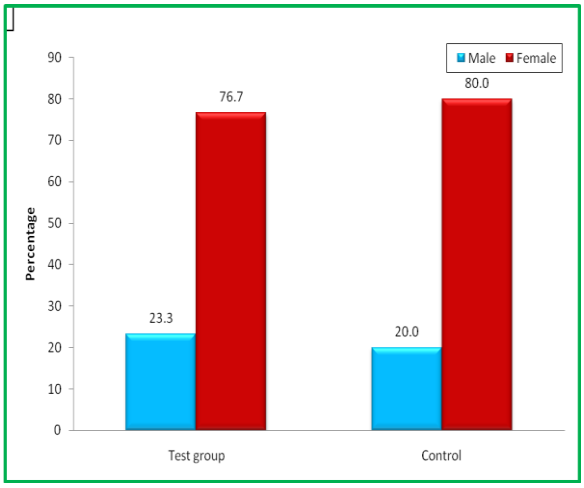

Figure 2: Showing Sex Distribution among Test and Control group (n=60)

Table.3: Showing Somnolence among Test and Control Groups (n=60)

Somnolence	Test group						Control						Significance of Test group vs Control group P- Value	
	Base line		30th day		60th day		Base line	30th day		60th day			Base line vs Base line	60th day vs 60th day
	No.	%age	No.	%age	No.	%age	No.	%age	No.	%age	No.	%age	0.106	0.008
Absent	1.00	3.33	3.00	10.00	5.00	16.67	0.00	0.00	7.00	23.33	14.00	46.67		
Mild	13.00	43.33	17.00	56.67	25.00	83.33	6.00	20.00	19.00	63.33	14.00	46.67		
Moderate	15.00	50.00	10.00	33.33	0.00	0.00	20.00	66.67	4.00	13.33	2.00	6.67		
Severe	1.00	3.33	0.00	0.00	0.00	0.00	4.00	13.33	0.00	0.00	0.00	0.00		
Total	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**		
Base line vs 60th day, Test applied: Wilcoxon signed rank test, P-value = <0.001*							**Base line vs 60th day, Test applied: Wilcoxon signed rank test, P- value = <0.001***							
n=60 Test used=Wilcoxon signed rank test.														
P<0.001 very significant with respect to base line verses 60th day in both test and control groups.														

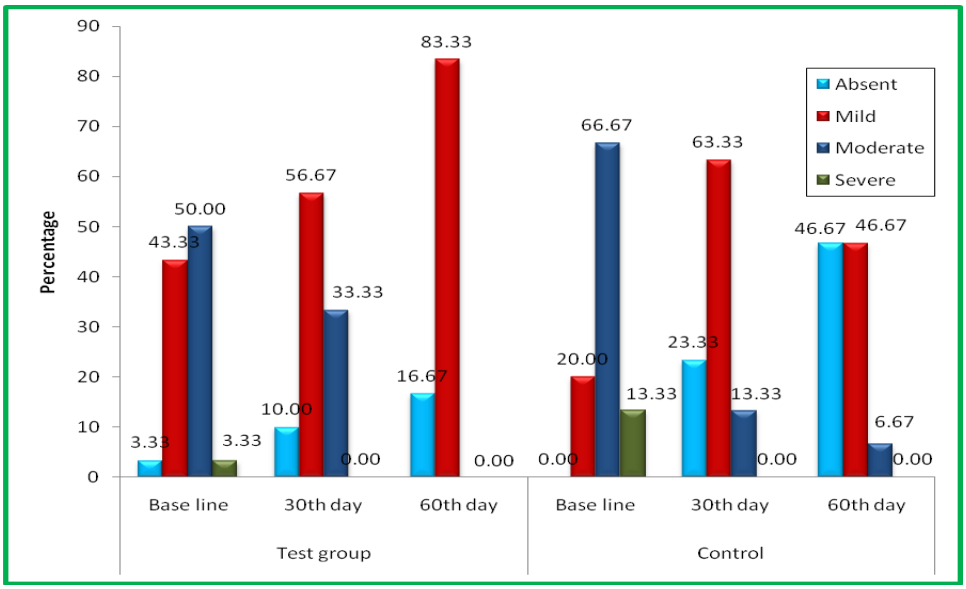

Figure.3: Showing Percent change in Somnolence among Test and Control Groups (n=60)

Table 4*: Showing Fatigue among Test group and Control group

									Significance of Test group vs Control group	
Fatigue	**Test group**				**control group**				**P- Value**	
	Base line		**60th day**		**Base line**		**60th day**		**Base line vs Base line**	**60th day vs 60th day**
	No.	**%age**	**No.**	**%age**	**No.**	**%age**	**No.**	**%age**	0.011	0.258
Absent	0.00	0.00	20.00	66.67	0.00	0.00	17.00	56.67		
Mild	5.00	16.67	10.00	33.33	0.00	0.00	10.00	33.33		
Moderate	23.00	76.67	0.00	0.00	23.00	76.67	3.00	10.00		
Severe	2.00	6.67	0.00	0.00	7.00	23.33	0.00	0.00		
Total	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**		
Test applied: Wilcoxon signed rank test, P-value = <0.001*					**Test applied: Wilcoxon signed rank test, P-value = <0.001***					
n=30 in test group and n=30 in control group										
Test used=Wilcoxon signed rank test										
P<0.001 very significant in both test and control groups with respect to base line verses 60th day.										

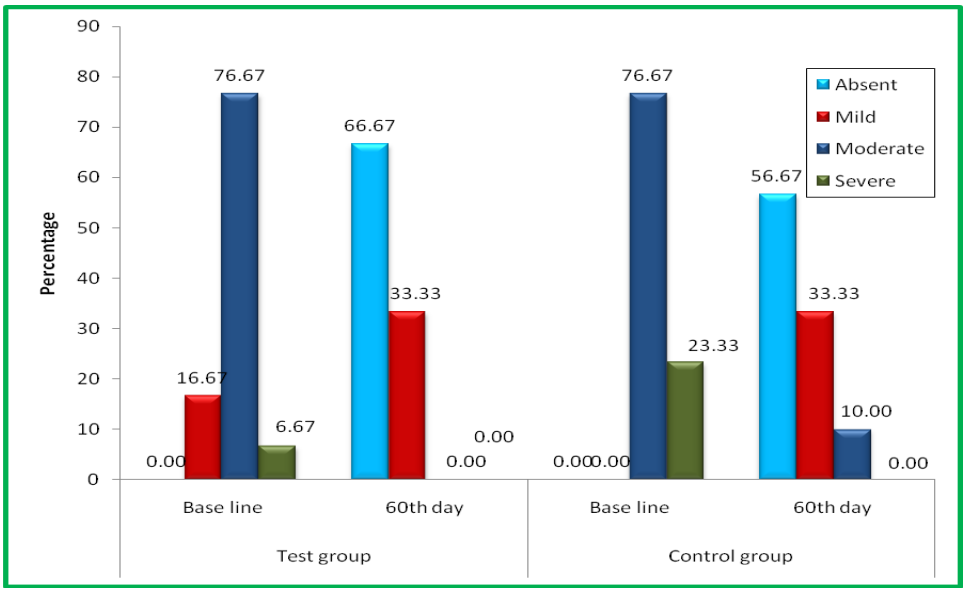

Figure.4: Showing Percent change in Fatigue among Test group and Control group (n=60)

Table 5: Showing Hypothermia among Test group and Control group (n=60)

													Significance of Test group vs Control group	
Hypothermia	**Test group**						**Control**						**P- Value**	
	Base line		**30th day**		**60th day**		**Base line**		**30th day**		**60th day**		**Base line vs Base line**	**60th day vs 60th day**
	No.	**%age**	**No.**	**%age**	**No.**	**%age**	**No.**	**%age**	**No.**	**%age**	**No.**	**%age**	0.005	0.706
Absent	8.00	26.67	17.00	56.67	25.00	83.33	13.00	43.33	24.00	80.00	27.00	90.00		
Mild	6.00	20.00	11.00	36.67	5.00	16.67	12.00	40.00	4.00	13.33	3.00	10.00		
Moderate	16.00	53.33	2.00	6.67	0.00	0.00	4.00	13.33	2.00	6.67	0.00	0.00		
Severe	0.00	0.00	0.00	0.00	0.00	0.00	1.00	3.33	0.00	0.00	0.00	0.00		
Total	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**		
Base line vs 60th day, Test applied: Wilcoxon signed rank test, P- value = <0.001*							**Base line vs 60th day, Test applied: Wilcoxon signed rank test, P- value = <0.001***							
n=30 in test group and n=30 in control group														
Test used= Wilcoxon signed rank test.														
P<0.001 very significant in both test and control groups with respect to base line verses 60 th day.														

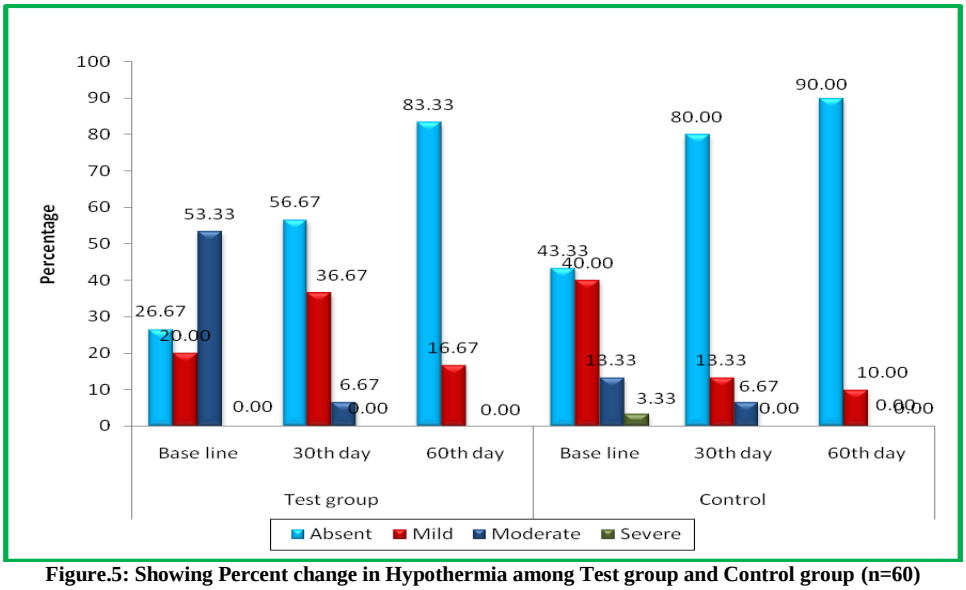

Figure.5: Showing Percent change in Hypothermia among Test group and Control group (n=60)

Table 6*: Showing Decreased Libido among Test group and Control group

													Significance of Test group vs Control group	
Decreased libidio	**Test group**						**Control group**						**P- Value**	
	Base line		**30th day**		**60th day**		**Base line**		**30th day**		**60th day**		**Base line vs Base line**	**60th day vs 60th day**
	No.	**%age**	**No.**	**%age**	**No.**	**%age**	**No.**	**%age**	**No.**	**%age**	**No.**	**%age**	0.891	0.11
Absent	19.00	63.33	19.00	63.33	28.00	93.33	16.00	53.33	16.00	53.33	23.00	76.67		
Mild	2.00	6.67	10.00	33.33	1.00	3.33	2.00	6.67	13.00	43.33	6.00	20.00		
Moderate	7.00	23.33	1.00	3.33	1.00	3.33	9.00	30.00	1.00	3.33	1.00	3.33		
Severe	2.00	6.67	0.00	0.00	0.00	0.00	3.00	10.00	0.00	0.00	0.00	0.00		
Total	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**		
Base line vs 60th day, Test applied: Wilcoxon signed rank test, P- value = 0.002							Base line vs 60th day, Test applied: Wilcoxon signed rank test, P- value = 0.004							
n=30 in test group and n=30 in control group														
Test used=Wilcoxon signed rank test														
P=0.002 very significant in test group with respect to base line verses 60th day. P=0.004 significant in control groups with respect to base line verses 60th day.														

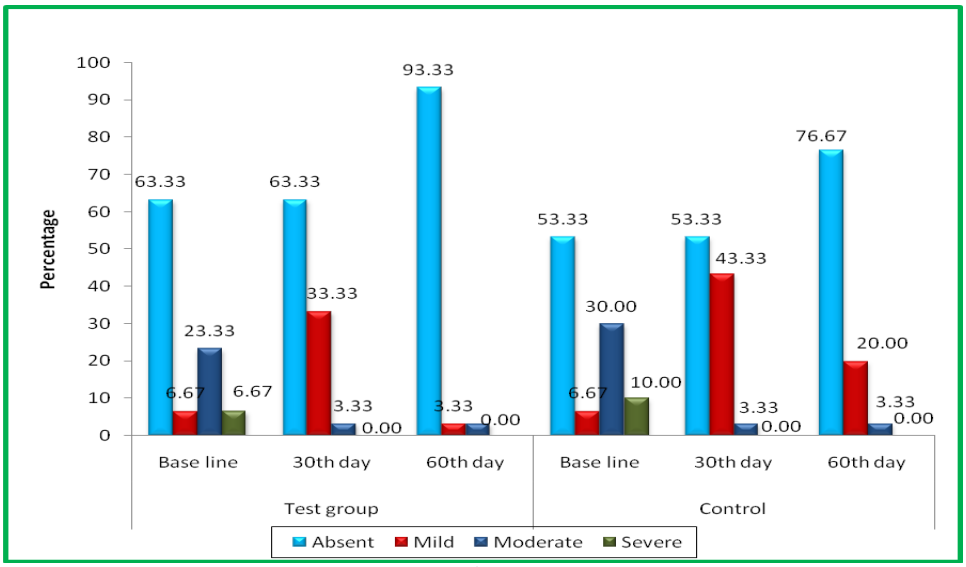

Figure 6: Showing Percent change in Loss of Libido among Test group and Control group

Table 7*: Showing Hoarseness of Voice among Test group and Control group

													Significance of Test group vs Control group	
Decreased libidio	**Test group**						**Control group**						**P- Value**	
	Base line		**30th day**		**60th day**		**Base line**		**30th day**		**60th day**		**Base line vs Base line**	**60th day vs 60th day**
	No.	**%age**	**No.**	**%age**	**No.**	**%age**	**No.**	**%age**	**No.**	**%age**	**No.**	**%age**	0.891	0.11
Absent	19.00	63.33	19.00	63.33	28.00	93.33	16.00	53.33	16.00	53.33	23.00	76.67		
Mild	2.00	6.67	10.00	33.33	1.00	3.33	2.00	6.67	13.00	43.33	6.00	20.00		
Moderate	7.00	23.33	1.00	3.33	1.00	3.33	9.00	30.00	1.00	3.33	1.00	3.33		
Severe	2.00	6.67	0.00	0.00	0.00	0.00	3.00	10.00	0.00	0.00	0.00	0.00		
Total	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**		
Base line vs 60th day, Test applied: Wilcoxon signed rank test, P- value = 0.002							**Base line vs 60th day, Test applied: Wilcoxon signed rank test, P- value = 0.004**							
n=30 in test group and n=30 in control group														
Test used=Wilcoxon signed rank test														
P<0.002 very significant in both test group P<0.004 in control group with respect to base line verses 60th day.														

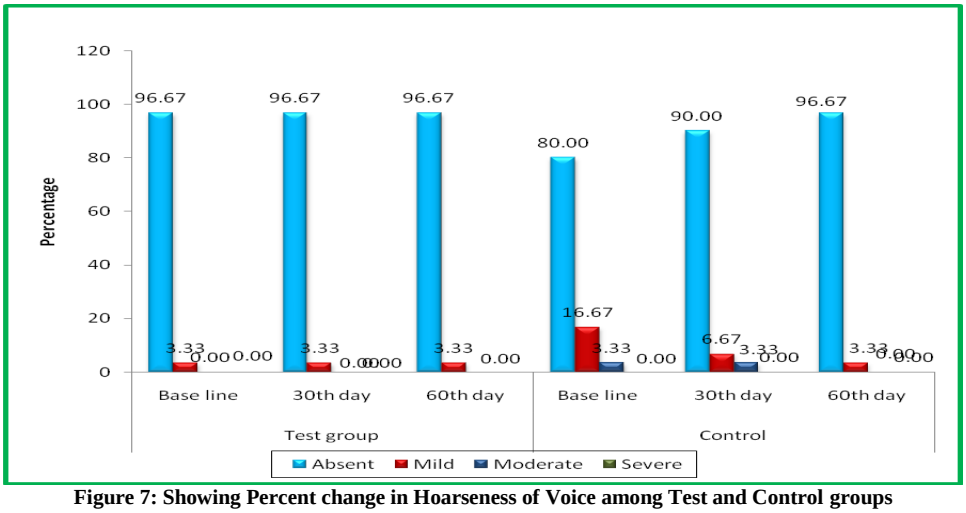

Figure 7: Showing Percent change in Hoarseness of Voice among Test and Control groups

Table.8*: Showing Puffiness of Face among Test group and control group

													Significance of Test group vs Control group	
Puffiness of face	**Test group**						**Control**						**P- Value**	
	Base line		**30th day**		**60th day**		**Base line**		**30th day**		**60th day**		**Base line vs Base line**	**60th day vs 60th day**
	No.	**%age**	**NO.**	**%age**	**NO.**	**%age**	**No.**	**%age**	**NO.**	**%age**	**NO.**	**%age**	0.899	0.612
Absent	10.00	33.33	22.00	73.33	29.00	96.67	11.00	36.67	21.00	70.00	27.00	90.00		
Mild	13.00	43.33	8.00	26.67	1.00	3.33	11.00	36.67	8.00	26.67	2.00	6.67		
Moderate	7.00	23.33	0.00	0.00	0.00	0.00	8.00	26.67	1.00	3.33	1.00	3.33		
Severe	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00		
Total	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**		
Base line vs 60th day, Test applied: Wilcoxon signed rank test, P- value = <0.001*							**Base line vs 60th day, Test applied: Wilcoxon signed rank test, P- value = <0.001***							
n=30 in test group and n=30 in control group														
Test used=Wilcoxon signed rank test														
P<0.001 very significant in test group P<0.001 in control group with respect to base line verses 60th day.														

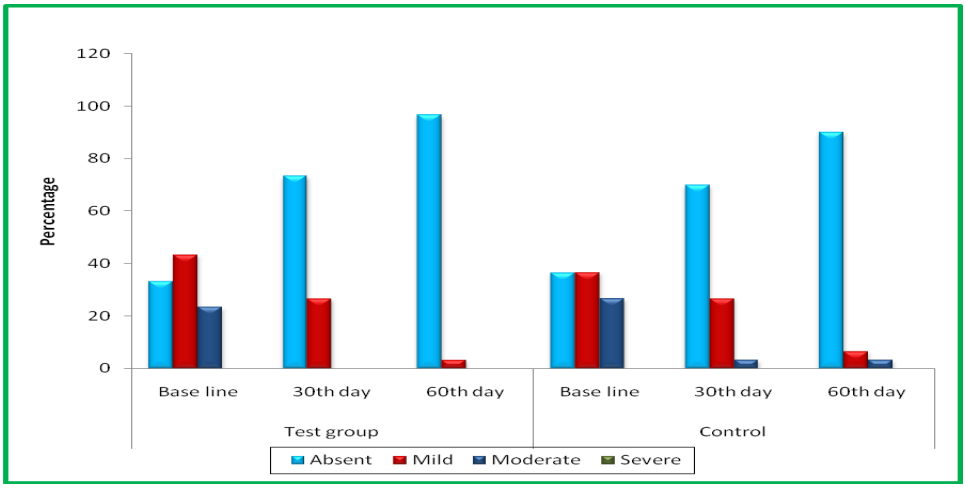

Figure.8: Showing Percent change in Puffiness of Face among Test and Control Groups

Table.9*: Showing Delayed Tendon Reflexes among Test group and Control group

													Significance of Test group vs Control group	
Delayed tendon Reflexes	**Test group**						**Control**						**P- Value**	
	Base line		**30th day**		**60th day**		**Base line**		**30th day**		**60th day**		**Base line vs Base line**	**60th day vs 60th day**
	No.	**%age**	**No.**	**%age**	**No.**	**%age**	**No.**	**%age**	**No.**	**%age**	**No.**	**%age**	0.574	1
Absent	12.00	40.00	13.00	43.33	13.00	43.33	10.00	33.33	11.00	36.67	13.00	43.33		
Mild	16.00	53.33	16.00	53.33	16.00	53.33	15.00	50.00	17.00	56.67	16.00	53.33		
Moderate	2.00	6.67	1.00	3.33	1.00	3.33	5.00	16.67	2.00	6.67	1.00	3.33		
Severe	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00		
Total	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**	**30.00**	**100.00**		
Base line vs 60th day, Test applied: Wilcoxon signed rank test, P- value = 0.157							**Base line vs 60th day, Test applied: Wilcoxon signed rank test, P- value = <0.02**							
n=30 in test group and n=30 in control group														
Test used=Wilcoxon signed rank test														
P<0.157 not significant in test group P<0.02 very significant incontrol group with respect to base line verses 60th day.														

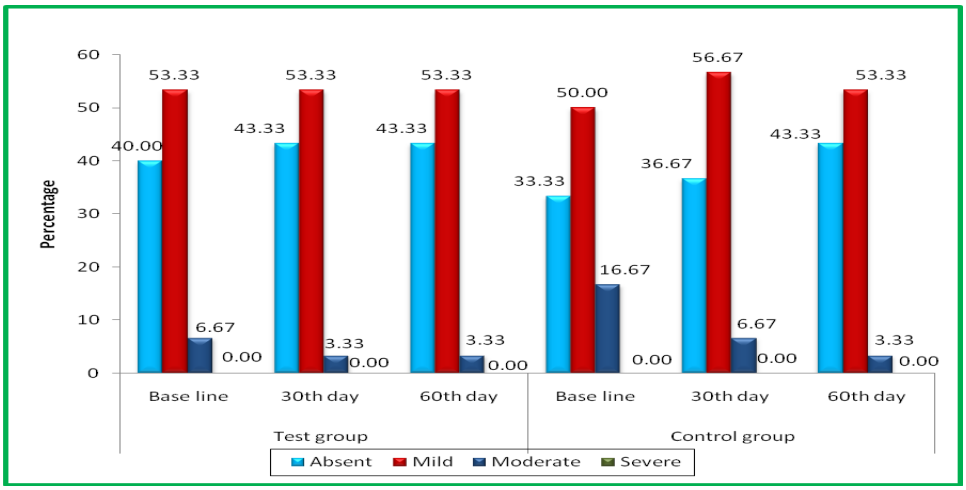

Figure.9: Showing Percent change in Delayed Tendon Reflexes among Test and Control groups

Table.10: Showing Triiodothyroxine among Test group and Control group (n=60)

Triodothyroxine (T3)	**Before Treatment**		**After Treatment**		**Percent change**	**P-value**
	Mean	**SD**	**Mean**	**SD**		
Test group	114.90	23.56	118.90	23.78	3.48	0.459
Control	105.51	24.60	113.10	14.84	7.19	0.055
P-value (Test group vs Control)	0.55					
n=30 in test group and n=30 in control group p=0.55 not significant						

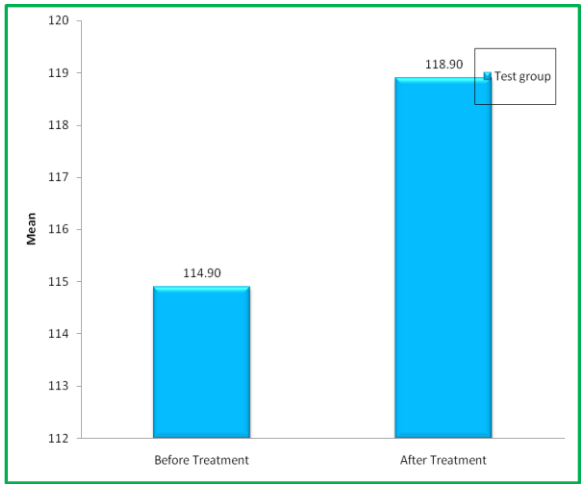

Figure.10: Showing Mean of Triiodothyroxine among Test and Control groups (n=60)

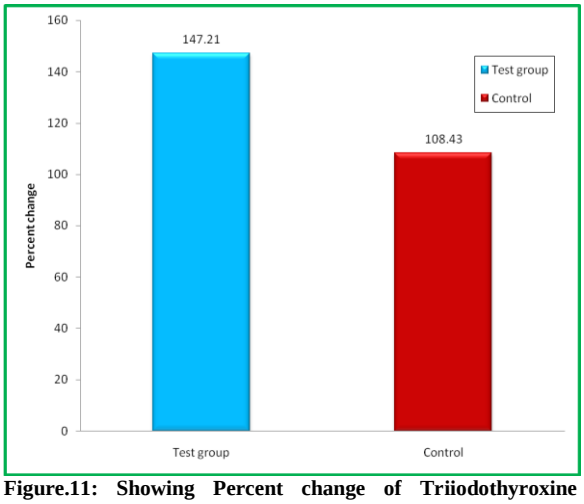

Figure.11: Showing Percent change of Triiodothyroxine among Test and Control groups (n=60)

Table.11: Showing Thyroxine among Test group and Control group (n=60)

T4	Before Treatment		After Treatment		Percent change	P-value
	Mean	SD	Mean	SD		
Test group	7.20	1.506	7.10	1.93	1.38	0.808
Control group	7.14	2.08	7.37	1.48	3.22	0.533
P-value (Test group vs Control group)	0.2874					
n=30 in test group and n=30 in control group p=0.2874 not significant						

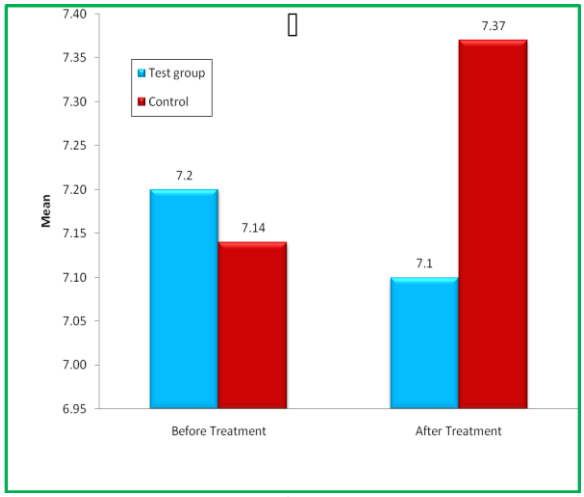

Figure.12: Showing Mean of Thyroxine among Test and Control groups (n=60)

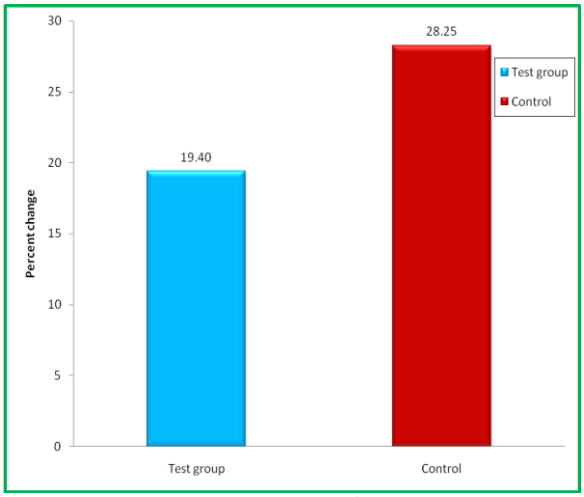

Figure.13: Showing Percent change of Thyroxine among Test and Control groups (n=60)

Table 12: Showing Thyroid Stimulating Hormone among Test group and Control group (n=60)

									Significance of Test group vs Control group	
TSH	**Test group**				**Control**				**P- Value**	
	Before treatment		**After treatment**		**Before treatment**		**After treatment**		**Before treatment vs Before treatment**	**After treatment vs After treatment**
	No	**%age**	**No**	**%age**	**No**	**%age**	**No**	**%age**	1	0.786
Normal	2.0	6.7	11.0	36.7	2.0	6.7	10.0	33.3		
Raised	28.0	93.3	19.0	63.3	28.0	93.3	20.0	66.7		
Total	**30.0**	**100.0**	**30.0**	**100.0**	**30.0**	**100.0**	**30.0**	**100.0**		
Mean±SD= 9.402±3.53			**Mean±SD= 7.93±4.37**		**Mean±SD= 16.10±6.72**		**Mean±SD= 7.55±4.705**			
Test applied: Mcnemar, P- value= <0.001*					**Test applied: Mcnemar, P- value= 0.004**					
n=30 in test group and n=30 in control group Test applied=Mcnemar's test P<0.001 very significant in test group with respect to before and after treatment P<0.004 significant in control group verses pre and post treatment.										

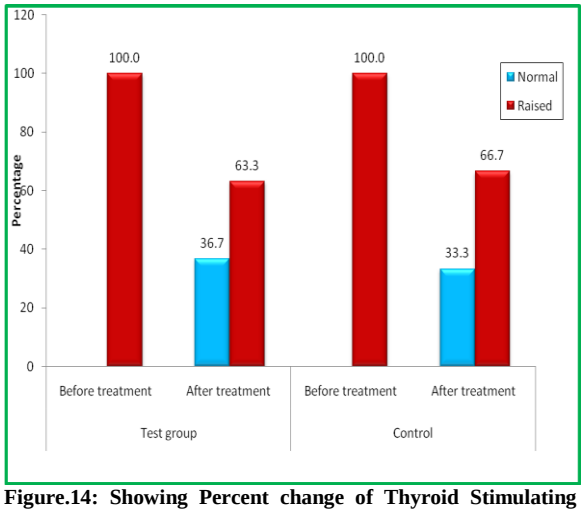

Figure.14: Showing Percent change of Thyroid Stimulating Hormone (TSH) among Test and Control groups (n=60)

DISCUSSION

The present study was conducted to evaluate the efficacy of a herbal *Unani* drug *Commiphora mukul (Muqil)* in the management of Primary Hypothyroidism. A total of 72 patients were enrolled for the study, out of those 8 didn't fulfilled the inclusion criteria and were excluded from the study.66 patients were randomly grouped and were allocated either test (Group A) or control (Group B) groups in equal distribution. During the treatment protocol,6 patients didn't complete the treatment course, and hence only 60 patients completed the treatment course with 30 in test group and 30 in control group. After the completion of treatment protocol of 60 days, statistical analysis was done.

Group A was given *Commiphora Mukul (Muqil)* in the form of powder in the dose of 1 gm twice daily after breakfast and after evening tea with warm water for a period of 60 days. Group B were given Tab. Thyroxine sodium 50 mcg orally once a day for a period of 60 days. The patients of both groups were followed up after every 15 days for a period of 60 days and recording of improvement in subjective and objective parameters were done on case record forms (CRF).

For statistical analysis, recorded data was compiled and entered in a spread sheet and then exported to data editor of SPSS version 20.0, Minitab version 14, and Graph pad prism software. The continuous variables like age and duration of disease were expressed in terms of (mean ± standard deviation) and categorical variables were expressed in terms of frequency and percentage. Student's independent t-test was employed for inter-group analysis of continuous data and for intra-group analysis paired t-test was applied. Wilcoxon signed rank test was used for intra group analysis of ordinal data. Chi-square test and Fisher's exact test was employed for inter group analysis of categorical data and for intra-group (before vs after) analysis of data categorical, McNemar's test was applied. The graphical representation of data was presented by means of bar graphs. A p-value of less than 0.05 was considered statistically significant.

The Mean ± SD for age of patients in test group was 38.4 ± 11.25 and 40.23 ±9.91 in control group. The difference in age of patients in test and control group was not significant (p=0.5) using paired "t" test. The age was analysed in both the groups which showed that hypothyroidism in the age group 36-45 years (33.3%), 15-25 years (23.3%), 46-60 years (23.3%) and 26-35 years (20%). which shows that hypothyroidism is more prevalent in 3rd & 4th decade of life.(Table.1/Figure.1)

As far as the sex is concerned, the disease is more common in females with 76.6% females and 23.3% males in test group and 80% females with 24% males in control group which clearly indicates the highest incidence in females. (Table.2/ Figure.2)

To evaluate the clinical efficacy of test and control drugs on various subjective and objective parameters like somnolence, fatigue, hoarseness of voice, puffiness of face, loss of libido, hypothermia, delayed tendon reflexes, arbitrary grading system was used with absent, mild, moderate and severe as 0,1,2,3 depending upon the severity of symptoms and signs. Clinical assessment was carried out on 0^{th},30^{th},60^{th} days respectively.

Somnolence is one of the symptoms of hypothyroidism. In the present study,

when the patients were assessed physically/clinically at base line, there was no significant difference between patients in test and control groups with respect to the different grades of somnolence parameter. After the treatment intervention, on last follow-up at 60th day, we found that there was a significant difference ($p<.05$) between the patients in test and control groups at different grades of somnolence using Wilcoxon signed rank test. It was observed that there was a significant difference in the test group with respect to somnolence since p value for patients at base line verses 60^{th} day was <.05 ($p<0.001$) and in control group the significance was almost the same.(Table 3/Figure.3) .

As far as fatigue is concerned the patients were assessed physically/clinically at base line, there was no significant difference between patients in test and control groups with respect to the different grades of fatigue parameter. After the treatment intervention, on last follow-up at 60th day, it was found that there was no significant difference ($p<0.258$) between the patients in test and control groups at different grades of somnolence using Wilcoxon signed rank test. It was observed that there was a significant difference in the test group with respect to fatigue since p value for patients at base line verses 60^{th} day was<.001 and in control group the significance was almost the same (Table.4/ Figure.4)

In case of hypothermia, the patients were assessed physically/clinically at base line for hypothermia, there was no significant difference between patients in test and control groups with respect to the different grades of hypothermia parameter. After the treatment intervention, on last follow-up at 60th day, it was found that there was no significant difference ($p<.706$) between the patients in test and control groups at different grades of hypothermia using Wilcoxon signed rank test. It was observed that there was a significant difference in the test group with respect to hypothermia since p value for patients at base line verses 60th day was <.05 ($p<0.001$) and in control group the significance was almost the same($p<0.001$). (Table.5/Figure.5)

Loss of libido is one of the symptoms of hypothyroidism. In the present study, it was found that, there was no significant difference between patients in test and control groups with respect to the different grades of loss of libido parameter at base line. After the treatment intervention, on last follow-up at 60th day, it was found that there was no significant difference ($p<.11$) between the patients in test and control groups at different grades of loss of libido using Wilcoxon signed rank test. It was observed that there was a significant difference in the test group with respect to libido since p value for patients at base line verses 60th day was <.05 ($p=0.002$) and in control group the significance was also significant($p=0.004$). (Table.6/Figure.6)

As far as Hoarseness of voice is concerned, there was no significant difference between patients in test and control groups with respect to the different grades of hoarseness of voice parameter at base line. After the treatment intervention, on last follow-up at 60th day, it was found that there was no significant difference ($p=1$) between the patients in test and control groups at different grades of using Wilcoxon signed rank test. It was observed that there was no significant difference in the test group with respect to hoarseness of voice since p value for patients at base line verses 60th day was >.05 ($p=1$) while as in control group it was significant ($p=0.034$). (Table .7/Figure.7)

It was observed that, there was no significant difference between patients in test and control groups with respect to the different grades of puffiness of face parameter at base level. After the treatment, on last follow-up at 60th day, it was found that there was no significant difference ($p=0.612$) between the patients in test and control groups at different grades of puffiness of face using Wilcoxon signed

rank test. It was observed that there was a highly significant difference in the test group with respect to puffiness of face since p value for patients at base line verses 60th day ($p<0.001$) in test group and in control group it was almost the same($p<0.001$). (Table .8/Figure.8)

As far as delayed tendon reflex is concerned, there was no significant difference between patients in test and control groups at base line. After treatment, on 60th day, there was no significant difference in both test and control groups ($p=1$). When statistical analysis using Wilcoxon signed rank test was used to assess the tendon reflex in test group patients, there was no significant difference in this parameter($p=0.157$) while in control group the difference was significant ($p<0.02$). (Table.9/Figure.9)

The Mean ± SD for T_3 in test group was 114.90±23.56 at baseline and 118.90 ±23.78 on 60th day, whereas in control group the Mean±SD score for T_3 was 105.51± 26.40 at baseline and 113.10 ± 14.84 at 60th day. When Mean±SD score for T_3 in both test and control group were compared statistically, it was found that the difference between the Mean ± SD score for T_3 at 60th day compared with baseline was not significant ($P>0.05$). (Table.10/ Figure.10,11)

The Mean±SD for T_4 in test group was 7.20 ± 1.506 at baseline and 7.10±1.93 on 60th day, whereas in control group the Mean±SD score for T_4 was 7.14±2.08 at baseline and 7.37±1.48 at 60th day. When Mean±SD score for T_4 in both test and control group were compared statistically, it was found that the difference between the Mean±SD score for T_4 at 60^{th} day compared with baseline was not significant ($P>0.05$). (Table.11/ Figure.12,13)

The Mean± SD for TSH in test group was 9.40 ±3.53 at baseline and 7.93 ± 4.37 on 60^{th}day,wheras in control group the Mean ± SD score for TSH was 16.10 ± 6.72 at baseline and 7.55± 4.705 at 60^{th}day. When Mean ± SD score for TSH in both test and control group were compared statistically using McNemar test, it was found that the difference between the Mean ±SD score for TSH at 60^{th} day compared with baseline was not significant ($P>0.05$). When the Mean±SD for TSH was compared with base line verses 60^{th} day in test groups, it was highly significant ($p=.001$) and in control group it was also significant ($p=.004$). (Table.12/Figure.1

Thus, from all these subjective, objective, safety parameters and statistical analysis, it has become evident that the test drug has significant effect on most of the subjective parameters as well as on Serum TSH levels. The test drug ***Muqil (Commiphora mukul)*** having actions like *muhallil waram* (anti-inflammatory), *mulayyin* (laxative), *mudirr-i-bawl* (diuretic), *mudirr-i-haiz* (emmenogogue), *kasir al-riyah*(carminative),*mufattit al-hasah* (lithotriptic), *muqaww-i al- bah* (aphrodisiac), *munafis al-balgham* (expectorant), *jail* (rubifacient), *musakhkhin* (calorific),*muqaww-iA'sab*(nervine tonic), *muhrik* A'sab (nerve stimulant) significantly improved the symptoms and signs of hypothyroidism such as somnolence, fatigue, hypothermia, libido, puffiness of face while its effect on hoarseness of voice and delayed tendon reflexes were insignificant.

The effects of test drug on lowering the raised Serum TSH are attributed to the thyroid activities of the test drug .Scientific studies have demonstrated that ***muqil*** activates the production of thyroid hormones Thyroxine (T_4), Triiodothyronine (T_3) , and improves the symptoms and signs of hypothyroidism. Its lipid lowering effect is also related to its thyroid activity.2-guggulestrone-a ketosteroid counteracts the thyroid suppressant activity of carbimazole. Its calorific (thermogenic) effect helps in cold intolerance of hypothyroid patients.

There was no toxic effect of either test or control dug on safety parameters. So it became evident that the test drug has significant effect on most of the subjective and objective parameters of hypothyroidism with no toxic effects on safety parameters.

Therefore, the test drug *Commiphora mukul (Muqil)* is safe, effective, economical and has wide pharmacological actions. The test drug *Commiphora mukul (Muqil)* as a single drug or *Unani* compound formulations having this drug as main constituent may be tried in such patients as an alternative.

CONCLUSION

Hence, it may be concluded that the test drug has significant effect on most of the subjective and objective parameters of primary hypothyroidism without having any toxic effect on any of the safety parameters. The sample size was small, so trials on larger sized samples needs to be carried out to further evaluate the efficacy of the drug on large scale. Therefore, the test drug *Commiphora mukul (Muqil)* is safe, effective, economical and has wide pharmacological actions. The drug *Commiphora mukul (Muqil) as* a single drug or *Unani* compound formulations having this drug as main constituent, may be tried in such patients as an alternative.

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