CLINICAL EVALUATION OF ALLOPATHIC AND CODED HERBAL MEDICINE (HYPOES) IN THE TREATMENT OF ESSENTIAL HYPERTENSIVE PATIENTS

Ph.D THESIS SUBMITTED

BY

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2015
IN THE NAME OF ALLAH, THE MOST GRACIOUS, THE MOST MERCIFUL
DEDICATED

TO MY

PARENTS & FAMILY
This thesis is submitted by Dr. Shah Nawaz Jamali in partial fulfillment of the requirements for the degree of doctor of philosophy in department of Pharmacology & Therapeutics, Faculty of Health & Medical Science, Hamdard University, Karachi in 2015.

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SUMMARY
The disease of high blood pressure is prevalent among all nations and countries across the world. In spite of having effective guidelines and recommendations this disease is still not being managed effectively. It is reported that in 50 million people of United States of America and around 1 billion patients suffers all over the world. The disease of high blood pressure causes many cardiac complications in hypertensive patients. With increasing pressure in vasculature, the risk of myocardial infarction, heart failure, stroke and renal failure increases many fold.

Various pathological factors have been identified as cause of this disease e.g., over activation of sympathetic system; increase the release of salt-retaining hormones and alterations in vasoconstrictor agents in blood vasculature. A part from this more intake of salt in diet and deficiencies in renin-angiotension aldosterone system may also play an important role in development of hypertensive disease.

With the introduction of ARBs in the treatment of hypertension more effective role has been found in the management of this disease. Candesartan Cilexetil is a newer ARB in treatment of hypertension with surmountable and long lasting control of blood pressure. It has been observed that Candesartan, an angiotensin II type 1 receptor blocker has been found more effective in newly diagnosed essential hypertensive patients in once daily dosage.

The basic purpose of this study was to evaluate the efficacy and safety of coded herbal medicine (HypoEss) in comparison with allopathic medicine (Candesartan Cilexetil) to control and treat hypertension disease. This study was comprised of (200) patients and was divided in to two groups; test drug HypoEss and control drug Candesartan. Test group was having (100) patients and received herbal combination treatment while; control patients received allopathic drug Candesartan (16mg) in remaining 100 patients. The patients were called fortnightly for follow up visits as to observe the parameters (Blood pressure, Lipid profile, renal functions and side-effects). The patients in this study received the treatment for minimum period of (90) days. The data was recorded in a tabulated form and analyzed statistically at the end of study duration.
In our research study the test group HypoEss was comprised of four herbal active ingredients administered for essential hypertensive patients which decreased mean systolic blood pressure 15.17% and diastolic blood pressure 18.07% percent in comparison to control drug Candesartan which decreased mean systolic blood pressure 20.56%, and a decrease of 21.65% was observed in mean diastolic blood pressure. The response in both parameters of blood pressure (systolic and diastolic) was observed statistically highly significant with (p<0.001) in case of both herbal versus allopathic treatment.

The effects of control drug on serum cholesterol, triglycerides and LDL-C were of nonsignificance statistically but the changes on serum HDL-C was observed significant in our findings. The efficacy of herbal drug on serum cholesterol and HDL-C levels were found unaltered statistically. However, significant changes were observed in serum triglycerides and LDL-C levels. The effects on triglycerides and LDL-C were found significant as (p<0.001).

The effect of control drug on serum urea and creatinine was observed decreased as 1.09 % in case of urea and 3.51 % in creatinine level. Where as no significant effect was found in case of serum urea and creatinine in test drug in present study.
TABLE OF CONTENTS

CHAPTER 1---
INTRODUCTION.................................................................01

1.1 Epidemiology of Hypertension.................................02
1.2 Hypertension in Pakistan and India...............................04
1.3 Hypertension its Socio-economic Impact.......................05
1.4 Hypertension the Basic facts.....................................06
1.5 Hypertension characterization....................................07
1.6 Classifications of high blood pressure.........................08
1.7 Diagnosis of high blood pressure...............................09
1.8 Essential hypertension...........................................09
1.9 Manifestation of High Blood pressure..........................09
1.10 Patho-physiology of Essential Hypertension................11
1.11 Hemodynamic factors in Essential Hypertension..............11
1.12 Resistant or refractory hypertension............................16
1.13 White-coat hypertension.........................................16
1.14 Factors in Pathogenesis of essential Hypertension............17
1.15 Early Detection & treatment of Hypertension..................22
1.16 Management of high blood pressure............................23
1.17 Patient’s Education................................................26

CHAPTER 2 ---- LITERATURE SEARCH.................................27

2.1 Impact and Significance of herbal plants in medicine.........28
2.2 Dorema ammoniacum D.Don........................................30
TABLE OF CONTENTS (Cont.)

2.6 Renin-Angiotensin System................................................................. 41
2.7 Angiotension Receptors...................................................................... 43
2.8 Candesartan Cilexetil........................................................................ 43

CHAPTER 3 ---- AIMS & OBJECTIVE OF STUDY................................. 47

3.1 Aim of study.................................................................................... 48
3.2 Objectives of the study................................................................. 48

CHAPTER 4---- METHODOLOGY............................................................. 50

4.1 Physical examination of study patients............................................ 51
4.2 Diagnosis and initial evaluation of patients..................................... 51
4.3 Inclusion criteria............................................................................... 52
4.4 Exclusion criteria ............................................................................. 52
4.5 Sample size....................................................................................... 52
4.6 Sample selection............................................................................... 53
4.7 Data collection.................................................................................. 53
4.8 Study limitations ............................................................................ 53
4.9 Statistical analysis ........................................................................... 53
4.10 Ethical issues................................................................................... 54
CHAPTER 5 ---
RESULTS.............................................................................................................................. 60

CHAPTER 6 ---
DISCUSSION..................................................................................................................... 80

CHAPTER 7 ---
CONCLUSION..................................................................................................................... 86

References.......................................................................................................................... 89
Appendices......................................................................................................................... 101
## LIST OF TABLES

<table>
<thead>
<tr>
<th>S.No</th>
<th>Title</th>
<th>Page No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Classification of blood pressure</td>
<td>8</td>
</tr>
<tr>
<td>1.2</td>
<td>Hypertension: patient’s awareness and control of disease.</td>
<td>10</td>
</tr>
<tr>
<td>1.3</td>
<td>Hypertension disease and suggested changes in life style patterns</td>
<td>15</td>
</tr>
<tr>
<td>1.4</td>
<td>Strategy guidelines to treat high blood pressure disease</td>
<td>25</td>
</tr>
<tr>
<td>5.1</td>
<td>Gender distribution of study participants</td>
<td>61</td>
</tr>
<tr>
<td>5.2</td>
<td>Distribution of Age groups in study patients</td>
<td>62</td>
</tr>
<tr>
<td>5.3</td>
<td>Changes in systolic blood pressure from day 0 to day 45 and day 65 90 With HypoEss and Candesartan.</td>
<td></td>
</tr>
<tr>
<td>5.4</td>
<td>Changes in diastolic blood pressure from day 0 to day 45 and day 90 with HypoEss and Candesartan.</td>
<td>67</td>
</tr>
<tr>
<td>5.5</td>
<td>Changes in serum Cholesterol from day 0 today 45 and day 90 in Patients of HypoEss and Candesartan groups.</td>
<td>68</td>
</tr>
<tr>
<td>5.6</td>
<td>Changes in serum Triglycerides from day 0 to day 45 and day 90 in patients of HypoEss and Candesartan groups.</td>
<td>70</td>
</tr>
<tr>
<td>5.7</td>
<td>Changes in serum LDL-C from day 0 to day 45 and day 90 in patients of HypoEss and Candesartan groups.</td>
<td>72</td>
</tr>
<tr>
<td>5.8</td>
<td>Changes in serum HDL-C from day 0 to day 45 and day 90 in patients of HypoEss and Candesartan groups.</td>
<td>73</td>
</tr>
<tr>
<td>5.9</td>
<td>Changes in serum Urea from day 0 to day 45 and day 90 in patients of HypoEss and Candesartan groups.</td>
<td>75</td>
</tr>
<tr>
<td>5.10</td>
<td>Changes in serum Creatinine from day 0 to day 45 and day 90 in patients of HypoEss and Candesartan groups.</td>
<td>76</td>
</tr>
<tr>
<td>5.11</td>
<td>Results of One way ANOVA.</td>
<td>78</td>
</tr>
<tr>
<td>5.12</td>
<td>Results of Wilcoxon Rank Sum test.</td>
<td>78</td>
</tr>
</tbody>
</table>
5.13 Observed and reported side-effects of study patients.

LIST OF FIGURES

<table>
<thead>
<tr>
<th>S.No</th>
<th>Title</th>
<th>Page No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Ischemic heart disease mortality rate</td>
<td>02</td>
</tr>
<tr>
<td>1.2</td>
<td>Prevalence of high blood pressure in adults</td>
<td>03</td>
</tr>
<tr>
<td>1.3</td>
<td>Patho-physiological factors in hypertension</td>
<td>07</td>
</tr>
<tr>
<td>1.4</td>
<td>Changes in microvasculature in hypertension disease</td>
<td>12</td>
</tr>
<tr>
<td>1.5</td>
<td>Role of sympathetic nervous system in regulation of B.P</td>
<td>17</td>
</tr>
<tr>
<td>1.6</td>
<td>Obesity induced hypertension</td>
<td>19</td>
</tr>
<tr>
<td>1.7</td>
<td>Hormonal and neural factors in hypertension</td>
<td>21</td>
</tr>
<tr>
<td>2.1</td>
<td>Leaves of Dorema ammoniacum D.don</td>
<td>30</td>
</tr>
<tr>
<td>2.2</td>
<td>Gum ammoniacum D.Don</td>
<td>32</td>
</tr>
<tr>
<td>2.3</td>
<td>Plant of Nepeta hindostana</td>
<td>33</td>
</tr>
<tr>
<td>2.4</td>
<td>Flowers of Nepeta hindostana</td>
<td>34</td>
</tr>
<tr>
<td>2.5</td>
<td>Rauwolfia serpentina with leaves and flowers</td>
<td>36</td>
</tr>
<tr>
<td>2.6</td>
<td>Fruit of Rauwolfia serpentina</td>
<td>37</td>
</tr>
<tr>
<td>2.7</td>
<td>Silkworm with hairy cocoons</td>
<td>39</td>
</tr>
<tr>
<td>2.8</td>
<td>Larvae of silkworm</td>
<td>40</td>
</tr>
<tr>
<td>2.9</td>
<td>Renin-angiotension-system (RAS)</td>
<td>42</td>
</tr>
<tr>
<td>2.10</td>
<td>Renin aldosterone system</td>
<td>42</td>
</tr>
<tr>
<td>2.11</td>
<td>Chemical structure of Candesartan Cilexetil</td>
<td>44</td>
</tr>
<tr>
<td>5.1</td>
<td>Gender distribution of study participants</td>
<td>62</td>
</tr>
<tr>
<td>5.2</td>
<td>Distribution of Age groups in study patients</td>
<td>63</td>
</tr>
<tr>
<td>5.3</td>
<td>IQR distribution</td>
<td>64</td>
</tr>
</tbody>
</table>
5.4 Changes in mean systolic blood pressure from day 0 to day 90 with HypoEss and Candesartan.

5.5 Changes in mean diastolic blood pressure from day 0 to day 90 with HypoEss and Candesartan.

### LIST OF FIGURES (Cont.)

<table>
<thead>
<tr>
<th>S.No</th>
<th>Title</th>
<th>Page No</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.6</td>
<td>Changes in serum Cholesterol from day 0 to day 45 and day 90 with HypoEss and Candesartan.</td>
<td>69</td>
</tr>
<tr>
<td>5.7</td>
<td>Changes in serum Triglycerides from day 0 to day 45 and day 90 with HypoEss and Candesartan group patients.</td>
<td>71</td>
</tr>
<tr>
<td>5.8</td>
<td>Changes in serum LDL-C from day 0 to day 45 and day 90 with HypoEss and Candesartan group patients.</td>
<td>72</td>
</tr>
<tr>
<td>5.9</td>
<td>Changes in serum HDL-C from day 0 to day 45 and day 90 with HypoEss and Candesartan.</td>
<td>74</td>
</tr>
<tr>
<td>5.10</td>
<td>Changes in serum Urea from day 0 to day 45 and day 90 in Patients of HypoEss and Candesartan group.</td>
<td>75</td>
</tr>
<tr>
<td>5.11</td>
<td>Changes in serum creatinine from day 0 to day 45 and day 90 with HypoEss and Candesartan group.</td>
<td>77</td>
</tr>
</tbody>
</table>
ABBREVIATIONS

B.P = Blood Pressure
JNC = Joint National Committee
US = United States
SBP = Systolic Blood Pressure
DBP = Diastolic Blood Pressure
TC = Total Cholesterol
TG = Triglycerides
LDL-C = Low Density Lipoprotein
HDL-C = High Density Lipoprotein
Chol = Cholesterol
HypoEss = Coded herbal medicine
Control drug = Allopathic medicine (Candesartan)
Mg/dl = Milligram per deciliter
% = Percentage
≤ = Less than or equals to
≥ = Greater than or equals to
DASH = Dietary approaches to stop hypertension
ISH = International Society of Hypertension
WHO = World Health Organization
mmHg = Millimeter of mercury
NO = Nitric Oxide
BMI = Body mass index
CVD = Cardiovascular disease
ACE = Angiotensin converting enzyme
ARB = Angiotensin receptor blocker
Hypt = Hypertension
AT-1 = Angiotensin type-1
AT-2 = Angiotensin type-2
IHD = Ischemic heart disease
d.f = Degree of freedom
S.D = Standard deviation
Σ = The Greek capital sigma denotes “sum of”
CAD = Coronary artery disease
ESRD = End stage Renal disease
CHAPTER – I

INTRODUCTION


1.1 EPIDEMIOLOGY OF HYPERTENSION

According to latest research updates 17 million deaths have been reported because of cardiovascular problems worldwide which is about one third of total deaths [1] among all cardiac manifestations. Whereas 9.4 million deaths have been documented as complications and issues related to high blood pressure [2]. Among all heart diseases 45% of deaths reported because of increased blood pressure. Fig-1.1 shows IHD, mortality rates. [3].

Fig-1.1: Ischemic heart disease mortality rates (WHO-2013)

A large number of people with high blood pressure have been observed and their number was increased from 600 million in 1980 to 1 billion in 2008. In 2008 worldwide, nearly 40% of adults who were aged 25 and above had been diagnosed as suffering from hypertension [4]. The percentage of high blood pressure was recorded more in African region with a percentage of 46% in comparison with a low prevalence in case of American region with a population of 35% respectively. Moreover a low prevalence was observed in high-income countries 35% in comparison to low-income countries 40% of patients suffered from hypertension [5].

It has been observed that the common reasons of increasing high blood pressure which attribute and aggravate the condition that have been cited in research articles and research seminars are; increasing population, the process of aging, behavioral factors such as unhealthy diet, excessive use of alcohol, less physical activity, more weight gain and continuous exposure to stress. The numbers of smoking people were 1 billion in 2008 and globally prevalence of obesity has been increased two times since 1980. A drastic increase has been documented in prevalence of high cholesterol 39% and of diabetes was 20% in adults in last couple of years. Tobacco use, improper and unhealthy diet, use of alcohol and no physical activity have been
observed as main reasons in causing noncommunicable diseases i.e. cardiovascular diseases, diabetes, chronic respiratory illness and cancers [6].

Cardiovascular related heart problems accounts for a major percentage of heart diseases globally. World Health Organization reported that in 1990; 5.2 million deaths were because of heart ailments in developed countries and 9.1 million deaths occurred in developing countries. The age related prevalence of high blood pressure of different countries has been given in Fig-1.2 [7].

![Fig-1.2: Prevalence of high blood pressure in adults.](image)

### 1.2 HYPERTENSION IN PAKISTAN AND INDIA

Statics regarding high blood pressure is of significance in a sense that it may help to manage high blood pressure disease and to chalk out policies to prevent it at initial stages. In literature and statics the term prevalence has been described to proportion of population who are managing their high blood pressure disease at a given time period. Whereas the term incidence related to number of new cases diagnosed every year. The social and physical pressure highlights the harmfulness and importance of hypertension in Pakistan. In a developing country like Pakistan the high blood pressure disease is common all over the country. The scientific approach and awareness of both the government and population is not up to mark. People ignore the anticipated risks and complications involved in hypertension. According to a national health survey government of Pakistan 70% of hypertensive patients does not under go for their treatment. In this regard the role of general physicians and health professional is also not satisfactory as they ignore the situation on the one side while, proper evaluation and diagnosis of patients is not according to international guidelines. In Pakistan high blood pressure affects
18% of adults over 15 years of age and 33% of adults over 45 years only 50% of all hypertensive patients are diagnosed and half of them are being treated to manage their disease. According to literature prevalence of hypertension disease in Pakistan estimated as 29, 26432 millions in an estimated population of 160, 19633 millions [8].

The situation of high blood pressure disease and its control is also unsatisfactory in India as well and it is quite alarming. It has been reported that out of 9.4 million deaths in India in 1990, cardiovascular disease accounted 2.3 million deaths that makes an average percentage of 25% of all deaths. Out of this 25 % 1.2 million people died because of coronary artery disease while 0.5 % of patients died due to stroke. This is also assumed that by the year 2020 the ratio of deaths due to heart problems may be doubled if this will happen than it may be more than 77% of china and 106% of all cardiac deaths in other Asian countries [9]. The reason probably seems to be lack of determination to control high blood pressure disease and lack of strategy to properly diagnose, treat and prevent hypertension. The facilitation to get access to hypertensive patients to health care facilities were also managed inadequately [10].

1.3 HYPERTENSION ITS SOCIO-ECONOMIC IMPACT

The countries with low resources suffer nearly 80% of their deaths due to heart related problems. These countries could not afford the economic impacts of ill health. The ratio of deaths is higher in lower income countries in comparison to those of developed countries. It has been anticipated that over the period of (2011-2025), the proposed economic burden of non-communicable diseases is to be 7.28 trillion US dollars in low and middle income countries. The low and middle income countries may suffer an annual loss of approximately 500 US dollars which is about 4% of gross domestic product in context of non-communicable diseases. Nearly half of this huge economic burden is incurred on cardiovascular diseases including high blood pressure [11].

As the under developing countries particularly with low income have been badly affected in their social and developmental determinants in case of their health, education and housing sectors. In this way it increases the risk of high blood pressure. For example, the stress of unemployment, the sense of being jobless, the fear of being homeless and improper facilities of medical and health related issues; all of these factors join together to influence high blood pressure.

Because of poverty and lack of awareness the timely detection and diagnosis of the disease and approaches to prevent its complications of high blood pressure is also neglected in low income and middle income countries. Poor performance in diagnostic procedures, improper medical treatment also increases the risk and approach to control high blood pressure in these countries. The shifting of people from villages and rural areas in a mass scale in low income and under development countries towards main cities and town also play an important factor in increasing blood pressure in these countries. This mass scale migration of people towards cities
created lot of problems in sense of resources in regard of health, education, housing and unhealthy environment in urban areas of low in- come countries.

This urbanization in main cities and towns encouraged consumption of fast food, sedentary behavior, excessive use of alcohol and harmful effects of tobacco that ultimately influence high blood pressure in these countries with low or no resources at all. Finally, it has also been documented in clinical research trials that the process of aging also increases blood pressure by stiffening of blood vessels this however can be slowed by healthy diet, fewer intakes of salt and carrying out regular physical exercise [12].

1.4 HYPERTENSION THE BASIC FACTS

High blood pressure involves the interplay of multiple neural, hormonal, renal and environmental factors. Despite effective treatment regimens the mortality among hypertensive subjects is much higher than that of normal individuals. Although reduction in clinic BP is an important and a major determinant in mortality reduction, several other factors influence survival in hypertensive patients. In cardiovascular system heart works as a pump as it beats it push blood to vasculature that carries it all parts of body. Blood pressure can be described as force of blood pushing against the walls of blood vessels (arteries) as it pumped by the heart. An increased or raised pressure of blood in arteries consistently becomes the main reason of developing high blood pressure in patients. If the pressure of blood is more in blood vessels the heart has to work hard to push this increased amount of blood in vasculature. If this condition is left untreated it may result into heart attack, enlargement of heart and ultimately into cardiac failure. If this high increased pressure of blood will not be addressed timely it may cause clotting of blood in arteries, weak spots in blood vessels.

Raised and continuous pressure of blood in vessels may result into leakage of blood into brain and this may develop the problem stroke which is difficult to treat. In research clinical trials it has been observed that high pressure of blood in vessels may play its role in causing kidney failure, blindness, and rupture of vessels and loss of mental activities. Blood always exert a pressure in vessels wall while it flowing blood through it. A person is diagnosed as hypertensive when the pressure in arteries is more than normal baseline limits. In medical sciences there is no more difference between hypertension and high blood pressure except two different terms for different situations. Hypertensive crisis is a severe increase in blood pressure and may harm the blood vessels and other organs. Various patho-physiological factors are involved in essential hypertension have been shown in Figure 1.3.
All hypertensive patients do not manifest symptoms at all, however, some patients may present with headache, lethargy, difficulty in breathing, stress, unrestlessness and some time may present nasal bleeding[13].

1.5 HYPERTENSION CHARACTERIZATION

Blood pressure is normally recorded by specific devices/apparatus and its unit is millimeter of mercury (mmHg). The blood pressure is consisted of two components the upper number and lower number. The systolic blood pressure is upper reading and is taken when heart contracts; while diastolic is pressure of vessels when heart muscle relaxes and this lower reading in recording. The lower is the pressure of blood in vessels; more cardiovascular harmful effects will be decreased for this outcome the systolic blood pressure shall be less than 105 mmHg and diastolic blood pressure shall be less than 60 mmHg in patients who have already been diagnosed as hypertensive. It is important to maintain blood pressure at a normal level for an adult that is systolic 120 mmHg and diastolic shall be 80 mmHg; otherwise it will harm the proper and normal functioning of organs like brain, heart and kidneys[14].

1.6 CLASSIFICATION OF HYPERTENSION

An understanding has been developed between following blood pressure monitoring and guide line providing agencies like, world health organization, international society of hypertension and
joint national commission on prevention, detection, evaluation and treatment of high blood pressure which is give as under in Table-1.1 [15].

Table-1.1: Blood Pressure Classification

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic B.P</th>
<th>Diastolic B.P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Pre-hypertension</td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Stage-I Hypertension</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage-II Hypertension</td>
<td>≥160</td>
<td>≥ 100</td>
</tr>
</tbody>
</table>

1.7 DIAGNOSIS OF HYPERTENSION

In present era of science and innovations; new electronic, mercury and aneroid devices have been introduced to measure blood pressure. The world health organization suggests that reliable and cost-effective electronic devices shall be introduced and must have manual controlled readings. WHO recommends that as mercury is toxic hence its use in blood pressure apparatus shall be discouraged in comparison to manual controlled blood pressure recording device. The aneroid device like sphygmomanometer if necessary to be used than has to be up to dated/calibrated every six months and users should be trained in its proper application of recording blood pressure. Before an initial diagnosis is made it is important to take blood pressure for several days particularly two times in a day ideally in morning and evening times is preferred [16].

1.8 ESSENTIAL HYPERTENSION

Essential hypertension is the most prevalent form of high blood pressure in all cases of hypertension. It is also known as primary hypertension in which other causes of high blood pressure like; Reno-vascular disease, adrenal medulla tumor (Pheochromocytoma), increase the release of aldosterone secretion, and other associated causes of hypertension of secondary reason shall be excluded. Irrespective of great advances in understanding its pathophysiology
and having latest treatment modalities. It has been noticed that in spite of all efforts the causes, risk factors of disease and its effective control is not up to mark and situation is getting worse than before in addressing this issue [17].

1.9 MANIFESTATIONS OF HIGH BLOOD PRESSURE

High blood pressure does not develop symptoms always. Most of diagnosed high blood pressure patients seldom develop symptoms. No doubt that the consequences of hypertension are really dangerous and symptom are infact warning signs to introduce lifestyle changes, dietary patterns and increase physical activities to decrease its complications. Sometimes hypertension may cause symptoms, such symptoms should be given priority, and neither can they be relied upon to signify hypertension. In most of diagnosed cases of high blood pressure it remains asymptomatic. It is important for hypertensive patients that on regular basis blood pressure recording shall be maintained and efforts be made to maintain it at normal ranges. In this regard various factors may play an important role in aggravation of increase in blood pressure of patients like smoking, stress, pollution, and obesity. Changes in patient’s life style pattern may be beneficial in their condition to improve it [18].

The findings of 3rd American National Health and Nutrition survey shows that the data of (1992 to 1995) reflects that 30% of all high blood pressure disease patients does not know about their disease condition, 15% of patients refuse to take medication, 26% received treatment but disease was un-controlled and only remaining 27% of hypertensive patients responded well in controlling their disease with anti-hypertensive treatment. This data has been implicated in table 1.2.

Table 1.2: Hypertension disease: Patients awareness and control of disease.

<table>
<thead>
<tr>
<th>National Health and Nutritional Examination Survey, Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information about disease</td>
</tr>
<tr>
<td>Drug Treatment</td>
</tr>
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1.10 PATHOPHYSIOLOGY OF ESSENTIAL HYPERTENSION

The exact pathophysiological mechanism of high blood pressure is still unclear, only 25% of patients have identifiable causes of their raised blood pressure either because of renal or adrenal gland related abnormalities this condition is called as secondary hypertension while, remaining 95% of patients have no known reasons of their disease and have been categorized as essential or primary hypertension. As many pathological factors play a vital role in development of hypertension and pathological alteration in them results in increasing blood pressure in high blood pressure patients. In essential hypertension there is a trend of being transmitted genetically in hypertensive families at a large. This results in appearance of abnormal syndromes with a biochemical and neurohormonal alterations at cellular levels. Various pathological causes have established in the genesis of hypertension as:

- Due to psychological stress over activation of sympathetic nervous system.
- Increased release and production of aldosterone and vasoconstricting agents.
- Intake of dietary sodium for a longer time period.
- Less dietary consumption of potassium and calcium.
- More secretion of rennin with an increased effect of angiotension II and aldosterone.
- Improper role of nitric oxide (NO), prostacyclines and natriuretic peptide.
- Alteration in kinin system to maintain vascular tone and salt related abnormalities in vessels [19].

1.11 HAEMODYNAMIC FACTORS IN ESSENTIAL HYPERTENSION

There are many factors which lead to cause resistance in blood vessels that ultimately results into structural thickening of vessel walls or vasoconstriction of vasculature. This structural thickening or vasoconstriction is main reason of developing essential hypertension. Because of intravascular endothelial abnormalities which may be because of endothelial dysfunction, increased oxidative stress and vascular alterations. This may aggravate high blood pressure and contribute to its pathogenesis [20]. Ischemia in high blood pressure patients may be influenced by small-vessel disease. It has been reported that endothelial dysfunction may result into small
arterial abnormality that result in to myocardial ischemia [21]. Changes in small vasculature during hypertensive disease have been reflected in Figure 1.4.

**Fig-1. 4: Changes in microvasculature in hypertension disease.**

**Identified causes of high blood pressure**
- Medication/ chemical induced
- Non-steroidal anti-inflammatory drugs; cyclooxygenase 2 inhibitors, Sympathomimetics, Oral contraceptives, Adrenal steroids, Cyclosporine, Renal or Reno vascular disease, Polycystic disease, Hydronephrosis, neoplasm.
- Primary Aldosteronism, Increased salt and water retention
- Pheochromocytoma (Tumor of adrenal medulla)
- Thyroid or Parathyroid disease (Grave’s disease, Thyrotoxicosis)
- Coarctation of aorta • Cushing syndrome.

**Contributory factors in hypertension**
- Overweight
- Excess alcohol consumption
- More intake of salt
- No regular physical activities
- Pollution as an environmental reason
Complications of hypertension

- Acute heart attack
- Enlargement of left ventricles
- Cardiac failure
- Severe chest pain
- Vascular disease
- Protein urea
- Renal impairments

Major cardiovascular risk factors

- Increases blood pressure
- Body mass index (BMI≥ 30)
- less physical activity
- deranged body lipids ▪ Diabetes Mellitus

In many research studies it has been observed that hypertension is a Continuous variable having no dividing line between normal and abnormal. It has also been reported that some people develop the disease of high blood pressure as they get older. This is not a healthy sign, because if people will live a healthy and active life the chances of getting hypertension will be less in comparison to an inactive lifestyle with abnormal eating habits.

Salt reduction

One of the important contributory factors in the development of high blood pressure is increase excess of salt intake than the normal recommended WHO guidelines. It has been observed in scientific literature that the intake of salt is higher in various countries and the intake is between 10-12mg/dl, in many the research articles it has been advised that a modest reduction of salt intake in daily life will decrease the risk and incidence of hypertension in already diagnosed hypertensive as well as normal population irrespective of ethnic, racial or age groups worldwide. The daily reduction of salt in routine life is one of the most important interventions to decrease cardiovascular disease and incidence of stroke worldwide at community levels [22].

The world health organization advised that a normal adult should consume at least 3,510 mg of potassium/ day. This potassium concentration may be achieved from daily intake of certain
vegetables like, spinach, cabbage, peas and beans. Similarly some fruits are also enriched with potassium like, papaya, bananas and date. However nuts also been mentioned as a rich source of potassium from diet point of view. Table 13 suggests lifestyle pattern to decrease blood pressure [23].

Table 1.3: Hypertension Disease and suggested changes in lifestyle pattern

<table>
<thead>
<tr>
<th>Change/modification</th>
<th>Suggestion</th>
<th>Approximate Decrease in (SBP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in body weight</td>
<td>Maintain (body mass index 18.5-24.9kg/m²)</td>
<td>6-20mmHg/10kg</td>
</tr>
<tr>
<td>Follow DASH diet plan</td>
<td>Eat a diet rich in fruits, vegetables, and low fat dairy products.</td>
<td>9-15mmHg</td>
</tr>
<tr>
<td>Salt reduction in daily diet</td>
<td>Decrease in dietary sodium intake to not more than 100mmol per day (2.4g sodium)</td>
<td>3-9mmHg</td>
</tr>
<tr>
<td>Regular physical activity</td>
<td>Participate in regular physical activity such as brisk walking (at least 30 min per day).</td>
<td>4-9mmHg</td>
</tr>
<tr>
<td>Low consumption of alcohol</td>
<td>Decrease intake to not more than 2 drinks (e.g. 24 oz beer, to 10 oz wine, or 3 oz 80-proff whiskey) per day</td>
<td>3-5mmHg</td>
</tr>
</tbody>
</table>

Dietary Approaches to Stop Hypertension (DASH), SBP, Systolic blood pressure. DBP, Diastolic blood pressure mmHg (millimeter of mercury).

1.12 RESISTANT OR REFRACTORY HYPERTENSION

Resistant, or refractory, hypertension is a different type of high blood pressure in which blood pressure does not come to normal ranges even been treated with two or more than two groups of medications[24]. It may be defined as a blood pressure of at least 140/90mm Hg or at least 130/80 mmHg in patients who were suffering from renal or diabetes. However, patients who were newly diagnosed as hypertensive’s or have not yet been started antihypertensive treatment should not be categorized as hypertensive regardless of their blood pressure levels.
Patients whose blood pressure are uncontrolled they have more chances to develop target-organ damage and more cardiovascular risk than controlled patients [25].

Following factors may be involved as main causative reasons in development of resistant hypertension:

- Improper recording of blood pressure.
- Excess intake of salt in daily diet
- Aldosteronism may cause excess retention of salt and water
- Improper medication with inadequate dosage
- Drug induced causative factor
- Drug resistant due to lack of rational drug therapy.[26]

1.13 WHITE COAT- HYPERTENSION

In some individuals it has been observed that their blood pressure gets increased during office times or working conditions but comes to normal ranges otherwise. This type of raised blood pressure has been categorized as white-coat hypertension. Blood pressure recording at home can help in identifying white-coat high blood pressure and prevent unnecessary treatment. This particular type of high blood pressure accounts in 20% of patients having sustained high blood pressure. However, it may work as a precursor of elevated blood pressure [27].

1.14 FACTORS INVOLVED IN PATHOGENESIS OF ESSENTIAL HYPERTENSION

Sympathetic nervous activity

Increased cardiac output with complain of increased heart rate may exhibit increased activity of sympathetic nervous system. This action may be more pronounced in younger hypertensive patients than aged patients. Apparently, it seems to be an increased release of catecholamine’s but correlation between increased catecholamine’s and increased blood pressure has not been of significance in research trials. There may be a role of oversensitivity of baroreceptor reflexes in stimulation of sympathetic nervous system. Once sympathetic system gets over stimulated it results in increased cardiac output and blood pressure by increased cardiac output and vasoconstriction of blood vessels. The sympathetic overstimulation also affects kidney functions by causing retention of salt and water Figure 1.5 gives role of sympathetic nervous system in regulation of blood pressure [28].
Defects in natriuresis

It has been observed that in some high blood pressure patients a defect is reported in their renal sodium balance. In cases of increased arterial pressure even controlled hypertensive patients increases their renal excretion of sodium in response to their raised blood pressure or to an increased sodium overload. Some chronic hypertensive patients also observe difficulty in maintaining their renal sodium balance.

Sodium and calcium

In essential hypertension there is an increased amount of intracellular sodium has been reported in blood cells and other tissues. This increased intracellular sodium may occur because of derangement in sodium-potassium exchange and other sodium transport mechanisms. Increased concentration of sodium inside cells will also increase the concentration of calcium inside cells as a result of facilitated exchange and might increase smooth muscle tone of vasculature that is accounted a an important factor in genesis of essential hypertension.

Factors exacerbating / aggravating hypertension

As the incidence and prevalence of hypertension is increasing; the focus of concerned authorities/ agencies involved in controlling high blood pressure is to identify the conditions and risk factors especially in high risk individuals to arrest and stop hypertension disease worldwide. Many predisposed aggravating factors in hypertension disease have already been reported that help in decreasing disease and make its treatment effective. Efforts have been focused on more consumption of vegetable, fruits and a proper healthy diet with a regular physical activity that
proved helpful not only decreasing blood pressure but also decrease its prevalence in communities at large [29].

**Obesity**

It has been suggested in research literature that weight reduction helps in decreasing blood pressure gradually. As with increasing body weight the chances of increasing intravascular volume may also be considered that influence cardiac activity directly or indirectly. Hence, it is recommended that weight shall be according to BMI normal ranges. Role of obesity in aggravating high blood pressure disease has been shown in Figure 1.6.

![Mechanisms of Obesity-Induced Hypertension](image)

**Fig- 1.6:** Obesity induced high blood pressure.

**Sodium intake**

There is still no consensus among health related professionals between the relationship of high blood pressure and intake of sodium salt. It has also been reported that a substantial increase in blood pressure has been noted not only in hypertensive’s but even in normal population with an ingestion of sodium more than 6gms; 100mmoles/dl [30].

**Alcohol consumption**

Alcohol also increases blood pressure by increasing catecholamine’s release and on chronic basis it causes retention of salt and water. The hypertensive patient who consumes more than 40 mg/dl ethanol per day is really seems difficult to bring his blood pressure within normal ranges.
Cigarette smoking
The effect of smoking on blood vessels is because of its neither increasing effect on nor-epinephrine levels. However, the prolong effect of smoking on blood pressure still have not been clear but the potentiating effect of smoking and hypertension on cardiovascular risks have been reported in literature.

Effect of exercise on blood pressure
It has been reported in clinical research trials that aerobic exercise may decrease blood pressure while, strenuous exercise in already active subjects has less effect on blood pressure. However, the interaction between blood pressure and exercise is variable and their immediate effect has not been reported.

Stress and hypertension
The relationship between stress and high blood pressure has been explained as stress increases sympathetic nervous system which in response increases excessive release of epinephrine and nor-epinephrine which has a direct stimulatory effect on heart and causes vasoconstriction by alpha adrenergic receptors both these effects increases blood pressure. As it has been reported in literature that the incidence of stress is greater in low socioeconomic groups of society hence the incidence of hypertension is more among them as compared to other groups of community.

Endothelial dysfunction
Vascular endothelial system produces a variety of chemical agents that act as local vasoactive compounds like nitric oxide which act as a vasodilator substance and peptide endothelin which may act as a vasoconstrictor substance in vascular system. Vascular endothelial compounds maintains cardiovascular regulation by releasing various chemical agents that works either vasodilator or vasoconstrictor agents of blood vessels. Abnormalities of this normal regulatory system of vasculature results in developing essential hypertension. Essential hypertension results because of impaired endothelial dependent vasodilatation and is mainly caused by release of free radicals from tissues that damage nitric oxide protective effect of blood vasculature. Therefore at present one of best option to treat essential hypertension is to modulate vascular endothelial system in decreasing complications of the disease.

Vasoactive substances
It has been reported in various research articles that some vasoactive agents plays an important role in maintenance of normal blood pressure. However, it has not been explained that by which exact mechanism they play their role in the development of essential hypertension. As the kinins particularly bradykinin works as an important vasodilator compound and is being inactivated by drug which inhibit angiotension formation pathways. Another important vasoactive substance
that has been recently discovered and is identified a strong vasoconstrictor agent in blood vessels may produce its effects because of salt induced stimulation.

**Hypercoagulability**

Many factors play their role in the coagulation of blood and alter blood physiology. The factors like, alteration in haemostatic factors as platelet activation, and fibrinolysis, changes in blood viscosity and blood flow; abnormalities that occur due to endothelial dysfunction collectively produce a hypercoaguable state that may precipitate high blood pressure disease. This problem can be addressed by timely management by antihypertensive treatment [31].

![Fig-1. 7: Hormonal and Neural factors in hypertension.](image)

**Hormonal factors**

There are many hormonal factors which play their in causing hypertension. The role of sympathetic hormones like, epinephrine and nor-epinephrine, the renin angiotension system like aldosterone, and atrial natriuretic peptide secreted from atria of heart produce their potent effects on heart and vascular system to increase blood pressure. As blood pressure changes throughout day and night irrespective of high or low levels of these hormones. Many interrelated mechanisms probably contribute to the control of blood pressure in man, the relative importance of salt-intake, the sympathetic nervous system, the rennin-angiotension system, vascular reactivity, neurogenic factors, the kidney and stress in determining the levels of
blood pressure play a vital role [32]. Various stimuli increasing hypertension has been mentioned in Figure 1.7.

**Genetic factors**

The role of genetics in development of high blood pressure cannot be dined at all. In some patients high blood pressure results from an interaction of complex genetic, environmental and demographic reasons. Thanks to new and innovative scientific techniques which have enabled health scientists to identify particular single gene by genome-wide linkage technology to separate single gene involved in the genesis of essential hypertension. It has been reported that there are many genetic loci involved in precipitating high blood pressure in hypertensive patients [33].

1.15 **EARLY DETECTION AND TREATMENT OF HYPERTENSION**

The early detection of hypertensive disease is not less than a blessing for hypertensive patients as the risk of complications of disease like acute heart attack, cardiac failure, stroke and chances of renal failure can be decreased to a great extent. Therefore, it has been recommended that adults should get monitored their blood pressure readings at frequent intervals. As now by invention of digital blood pressure recording devices the measurement of blood pressure has been possible outside clinic settings. In case of early diagnosis of the disease the patient should consult concerned health professional as all patients does not get benefited from changes in their life-style modifications.

1.16 **MANAGEMENT OF HYPERTENSION**

According to latest updated report of the Joint National Committee (JNC-VIII, 2013) on Prevention, Detection, Evaluation, and Treatment of increased blood Pressure has highlighted the new recommendations for prevention and treatment of high blood pressure following are key points of guidelines:

- In a person of age more than 50 years the systolic blood pressure of greater than 140 mm Hg has been described as a main cardiovascular risk factor than diastolic blood pressure.
- The concept of prehypertension has been emphasized in manner that people having a systolic blood pressure of 120-139 mm Hg or a diastolic blood pressure of 80-89 mmHg should be diagnosed as prehypertensive and be advised to follow lifestyle modifications as to decrease the risk of cardiovascular disease.
The effectiveness and success of drug intervention will also depend upon increasing awareness in hypertensive patients and by building trust between patients and health professionals.

However, according to British Hypertension Society recommendations to control high blood pressure following outlines has been suggested:

- It will be better to utilize the resources on primary prevention of high blood pressure rather than inappropriate use of medicines. Hypertensive patients and people at large shall be recommended to engage themselves in carrying out healthy physical activities in their routine schedules.
- Efforts shall be made on detection and early diagnosis of hypertension in its initial stages on population.
- Strategy shall be designed to propagate public awareness regarding anticipated complications and economic constraints about the disease of high blood pressure.
- Consider the role of aspirin and statin in decreasing risks of cardiovascular disease.
- The importance of drug medication shall be realized at large for proper treatment and control of disease.

The patients who are already diagnosed as diabetics or kidney disease the objective of treating them is to decrease their blood pressure less than 130/80 mmHg. Many clinical research studies of placebo-controlled and drug intervention in cases of mild to moderate high blood pressure have shown a decrease in heart and renal complications and cases of death with drug treatment. At present more effective and safe drug groups are available to combat the disease. The key to control and manage the problem of high blood pressure disease by adopting life style changes and with cost-effective antihypertensive medications.
Table- 1.4: Strategy guidelines to treat high blood pressure disease.

Changes in lifestyle pattern

If blood pressure is (<140/90mmHg)
(<130/80mmHg in diabetics or renal disease)
1.17: Patient’s Education about control of disease.

- Educate patients understanding about high blood pressure disease recognition.
- With experience and scientific reasoning try to clarify patient misunderstandings about the disease of high blood pressure.
- Inform about the readings/recorded values of blood pressure and give him a written copy about the diagnosis of his disease.
- Discuss with patient as to make him agreed to understand goal blood pressure.
• Inform and guide the patient about the anticipated complication and risk factor involved in drug treatment is ignored.
• Discuss with patient the role of drug treatment, its effectiveness and safety profile.
• Suggest patient to keep continue on regular physical activity, follow recommended diet plan and less consumption of salt and alcohol.
• Emphasize patient to continue drug treatment because free of symptoms did not mean cure of disease.
• Blood pressure cannot be felt nor be though upon hence, must be measured with regular time intervals.
• Early detection of disease and its immediate treatment is a blessing for patient. (WHO guidelines for Hypertension 2003)
2.1 Impact and significance of herbal plants in medicine

The significance of herbal medicine in the treatment of various diseases cannot be ignored at all. The herbal or unani mode of treatment is famous across the world and has attracted a large proportion of population but it is also anticipated that the efficacy and safety must be scientifically accomplished for a larger benefit of people. This type of treatment usually given in combination form as to get more magnitude of response in comparison to a single ingredient. The trend of people towards herbal treatment is increasing with the passage of time but on the other hand it is hoped that quality control shall be taken into account as far as its efficacy and safety is concerned [35].
Plants as herbal medicines are manufactured on commercial basis on a larger scale 25% of all medicines across the world comes from plant sources and these are preferred mode of treatment. Alternative medicinal therapy to conventional pharmaceuticals works as a complimentary medicine to treat disease [36].

In India more than 70% of the population uses herbal drugs for their health. Ayurvedic medicine and traditional medicine are being practiced on scientific grounds. In Pakistan the trend is growing towards the use of herbal medicine for treatment of various diseases. These herbal drugs known as unani medicine or eastern medicine are rich sources of beneficial chemical constituents exerting bioactivity. Newer approaches utilizing research and technology in combination with the traditional medicine will yield rich dividends to improve health. Therefore, strategies are being developed to design new herbal products so that it can prevent disease particularly infectious diseases to combat microbial resistance. Attempts are being made to facilitate patients in treatment as well as to prevent them with effective and safe herbal medicines in future as well. Herbal treatment has attracted peoples because of this assumption that it is safe and no side-effect is anticipated in comparison to allopathic mode of treatment. Herbal medicines are costeffective and economical from cost point of view.

The role of herbal medicine in the field of health sciences has been increased many fold at present scenario of high incidence and prevalence ratio of hypertension all over the world. Approximately 18-20% of world population is affected from this disease. The discovery of new herbal plants and their efficacy in terms of disease prevention and control is anticipated as to provide an alternative option for these patients. The safety and efficacy shall be evidence based and cost effective for a larger proportion of population across the world. The trend of people toward natural compounds may also require the latest scientific approaches in the management of this disease with all efforts to decrease present prevailing rate of high blood pressure in various nations and communities altogether.
LITERATURE SEARCH ON HYPOESS

The coded herbal formulation (HypoEss) for essential hypertension treatment comprises of following herbal components:

- *Dorema ammoniacum* D Don.
- *Nepeta hindostana* L.
- *Rauwolfia serpentina* L (Benth).
- *Bombyx mori* (Silk Worm).

2.2 DOREMA AMMONIACUM D. DON.

English name: Ammoniacum, Vernacular name: (Daroonaj Aqrabi), Family: Umbelliferae/ Apiaceae, Distribution: W. Asia – Iran to Afghanistan and Pakistan, Part used: *Gum resin* [37]. Leaves of Dorema ammoniacum has been reflected in Figure 2.1.

![Figure-2.1: leaves of Dorema ammoniacum.](image)
Description
A tall perennial shrub, 2-3 m tall, branched, stem base 6-12 cm in diameter, woody, radical leaves large, ternatisect, leaf segments large, oblong, obtuse, leaf base in amplexicaul umbel, simple on branches, peduncles 1-2 cm long; involucres of 5-8 small linear bracts, calyx teeth minute, petals white, fruit elliptic to oblong, 6-8 mm, 4-5 mm broad, glabrous, dorsal compressed; dorsal and intermediate ridges are distinct, thin and lateral ridges broad; furrows 1-vittate; commissure 4-vittate.

Occurrence
Native of Iran and surrounding regions. In Pakistan, it is distributed in Baluchistan. Also found in Afghanistan [38].

Active Constituents
Volatile oil, salicylic acid, valeric acid and butyric acid [39].

Temperament
Warm and dry in second order.

Functions and Properties
It is used in catarrh, asthma, chronic bronchitis and enlargement of liver and spleen, when applied externally, it acts as mild irritant. The resin is employed in perfumery. The gum has found with mild diuretic action. This may work as antispasmodic and helpful in removing swellings and pain due to sprain, and joint problems. To open or break the piles applied over them in past, in ringworm, vitiliginous and leucodermal patches dissolved in vinegar and applied as embrocating. Applied on wounds as ointment.

In chronic cough and asthma mixed with honey and administered as linctus. It is also effective in dyspnoea. To get rid of the putrefaction and smell of phlegm and to get rid of its excess, it is of value as expectorant and purgative of phlegm. In diphtheria, splenic hardness or inflammation, epilepsy, paralysis, facial paralysis, spasmodic affections, rheumatism and gout administered or applied with suitable drugs. It has been used as emmenagogue and expellant of dead fetus and to cause requisite early abortion. As anthelmintic the gum-ammoniac is also very useful [40]. Gum ammoniacum from Dorema ammoniacum has been shown in Figure 2.2.
Pharmacological Activity
Stimulant, expectorant, antispasmodic, Resolvent of hard swellings and inflammations [41], diuretic, emmenagogue, aperients and anticonvulsant [42].

Taste and Odour
Bitter, somewhat acrid taste and balsamic odour [43].

Dosage
2 grams

Side Effects
Large doses or long term use may cause' haematuria [44].

Corrigent / Antidote
*Pimpinella anisum* Linn. (*Anisun*), Vinegar [45].

2.3 NEPETA HINDOSTANA L.
English name: Nepeta herb, Vernacular name: (Badranjboya), Family: Labiatae, Distribution: Nepal, Pakistan, India, and Afghanistan. Part used: Whole herb [46]. The plant of Nepeta hindostana L has been shown in Figure 2.3.

Figure-2.3: Plant of Nepeta hindostana

Description
An erect or ascending herb, 15-40cm, high leaves broadly ovate or orbicular, crenate.
Flowers blue-purple, nutlets broadly oblong, brown with white dots [47].

Active Constituents
Nehipetol, nehipediol, stigmasterol, β-sitosterol, dinatin, nepetin, nepetinin, 6-hydroxyluteolin and 7, 4-0-dimethyl scutellarein [54], d- and l-limonene, methyl-heptenone, citronellal, l-menthone, citronellol, geraniol and geranyl acetate [48]. The flowers of Nepeta hindostana L has been given in Figure 2.4.

Temperament
Warm and dry in second order [49].
Functions and Properties
The leaves and stems are good for insanity, giddiness, hiccups, dyspnoea, bronchitis, griping, muscular pain, asthma, tuberculous glands, headache, and scabies. Decoction of the leaves is used for toothache as gargle and as tonic for cardiac function. Its paste is effective against rheumatic pains and breast inflammations. Fruit is a brain tonic and useful in hypochondriac conditions.

Plant infusion and gargles are considered useful in strengthening the gums and to remove malodor from mouth. The syrup and aqua are frequently administered for atrabilious and phlegmatic disorders. The plant is also used in fevers, gonorrhea, and decoction for sore throat [50]. It also acts as a blood purifier and useful in chest and back pain [51].

Pharmacological Activity
Exhilarant, carminative, stomachic, resolvent, sedative, antipyretic, and diaphoretic, cardiac tonic. The herb in a preparation (LIPOTAB) has shown significant antihypercholesterolemic and hypotensive effects in clinical and experimental studies [52].

Taste and Odour
Slightly bitter, aromatic [53].

Dosage
3 grams

**Side Effects**
Contra-indicated in patients suffering from ailments of pelvic region.

**Corrigent / Antidote**
*Boswellia glabra* Linn. (*Kundar*), Tragacanth, Gum acacia [54].

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2.4 **RAUWOLFIA SERPENTINA (L.) BENTH. EX KURZ**

English name: Serpentine root, Vernacular name: (Asrol), Family: Apocynaceae,
Distribution: Brazil, Nepal, Pakistan, India, China, Germany, France, Indonesia, Italy, Japan, Korea, Mexico, Sri-Lanka Russia, Turkey, England and U.S.A., Part used: Root, root extracts, leaves [55]. Rauwolfia serpentina with flowers is given in Figure 2.5.
Figure-2.5: Rauwolfia serpentina with leaves and flowers.

Description
A small shrub 50-60cm high, branches simple and glabrous. Leaves whorled, usually three, ovate-lanceolate, elliptic-lanceolate, entire, dark green above and plae green beneath, inflorescence terminal or axillary, flowers pink or reddish-pink. Fruit red, ovoid pointed turning to shining black when fully mature. The drug occurs in cylindrical or slightly tapering, tortuous pieces 2-10 cm long, 5-22 mm in diameter. Outer surface is grayish-yellow, light brown or brown [56].

Active Constituents
The major constituents include: ajmaline, ajmalinine, ajmalicine, serpentine, serpentinine, ophioxylin, reserpine [57].

Temperament
Cold and dry in third order.

Functions and Properties
The root is used in insanity, hysteria, hypertension, epilepsy, and insomnia, painful affections of the bowels, dysentery, hypochondria and irritative conditions of the central nervous system. Bruised root applied on the site of poisonous insect bite instantly gives relief. Decoction of the root has been given to increase uterine contractions and to promote expulsion of the fetus. With Andrographis paniculata Nees. (Kiryat) ginger and black salt it is used in fevers. With Aristolochia indica (Isharmul) it is given in cholera and colic. The extract or juice of leaves of Rauwolfia serpentina is applied on eye to get relief from corneal opacity.
Pharmacological Activity
Antihypertensive, hypnotic, anthelmintic. As the extract of Rauwolfia serpentina contains an active ingredient which resembles reserpine that has an inhibitory effect on central nervous system. This compound may also produce sedation and decreases blood pressure by inhibition of vasomotor centre along with decrease heart rate of hypertensive patients. The reserpine also exhibits respiratory inhibition, stimulation of peristalsis, myosis and relaxation of nictating membrane. Serpentine possesses antifibrillar activity. It markedly inhibited the succinate dehydrogenase activity in brain and liver tissues. Ajmaline has been reported to stimulate respiration and intestinal movements. Ajmalicine possesses a central depressant activity in addition to its adrenergic blocking action [58]. The fruit of Rauwolfia serpentina has been given in Figure 2.6.

Figure-2.6: Fruit of Rauwolfia serpentina

Taste and Odour
Roots are of sharp bitter taste, odourless [59].

Dosage
2 grams

Side Effects
In large doses it may produce deep sleep where the reflexes and sensation of pain are (totally) diminished and death may result from asphyxia due to paralysis of respiratory centers. Excessive use may cause irritation in the alimentary canal and vomiting [60].

Corrigent / Antidote
Dephinium denudatum wall. (Jadwar), Piper nigrum Linn. (Filfil Siyah) [61].
2.5 BOMBYX MORI (SILK WORM)

Bombyx mori belongs to kingdom of Animalia, phylum: Arthropoda, it is included in class insect and by order has been put into in the list of Lepidoptera vernacular name: (Abresham). It belongs to family; Bombycidae [62]. The silk worm with hairy cocoons has been shown in Figure 2.7.
Development
As all lepidopteron silk worm also possess strong appetite. They keep busy in eating day and night. About ten days are required eggs to hatch. When the color of their head turns to darker; it is time for them to molt [63]. In a cocoon of this raw silk is produced in salivary glands that protects them during their of motionless movement raw silk the larvae enclose themselves [64].

Scientific and medical uses
Silk worm have important medical and scientific applications in medical profession it play significant role in understanding and functions of hormones, pheromones. It also been applied in understanding of physiology of brain and its structures. It in various studies its role in hypertension has been reported [65]. At present new strategies are being applied on genetic engineering and genetics of silkworm [66, 67]. The larvae stage of silk worm has been given in Figure 2.8.
Many projects have worked on genetic engineering of silkworms to produce desirable proteins in the place of silk. Such proteins include human drugs [68]. The Bombyx mori now has been reported with an effective role in understanding structures and anatomical contents of human body. It is being tested in having an important role in endocrinology and its anomalies. In manufacturing new chemicals for treatment approaches silk worm is under experimental process.

2.6 RENIN ANGIOTENSIN SYSTEM AND BLOOD PRESSURE

The renin angiotensin system is the most important endocrine system that maintains blood pressure by releasing rennin from kidneys in response to low renal perfusion or a decreased salt intake. Rennin may also be secreted in response to sympathetic nervous system stimulation. It is the chemical substance rennin which converts angiotensinogen to angiotensin I which is physiologically inactive compound and is rapidly converted to angiotensin II in the lungs by
angiotensin converting enzyme (ACE) inhibitors. As angiotensin II is strong vasoconstrictor and increases blood pressure. A part from it increases vasoconstriction this angiotensin system increases the secretion of salt retaining hormone aldosterone from adrenal gland which further enhances the increase in salt and water reabsorption which increases blood pressure. However, in some studies it has been associated that the renin in blood circulation is not directly involved in increasing blood pressure in essential hypertensive patients [69]. The exact mechanism of renin angiotensin system in maintenance of blood pressure is still under research. The research clinical trials have reported that around 20-30% of patients diagnosed as essential hypertensive patients have been observed as having increased plasma rennin levels [70]. As far as its adverse effects on the damage of vital organs and heart related complications are concerned it depends on degree and extent of activation of this system. [71]. From physiological point of view the vasoconstricting effect of renin angiotensin system plays an important role in understanding the patho-physiology of cardiovascular disease [72].

It is well documented that drugs act on angiotension formation pathway (ACE, EC 3.4.15.1) gene polymorphisms are associated with various diseases such as hypertension, heart vasculature, myocardial infarction and changes in blood glucose levels. Renin angiotensin aldosterone mechanism also plays a significant role in the development of high blood pressure disease as shown in Figure 2.9 [73].

![Fig-2.9: Effect of Renin Angiotensin System on blood pressure.](image-url)
The renin-angiotensin system, which regulates blood pressure, plays an important role in the pathogenesis of coronary artery disease. Several have reported that gene polymorphisms also involved in development and progression of cardiovascular disease [74]. The step of changes in aggravating blood pressure by renin-angiotensin-aldosterone system has been reflected in Figure 2.10.

![Renin-angiotensin-aldosterone system](image)

**Fig-2.10: Renin- Angiotensin- Aldosterone System**

### 2.7 ANGIOTENSIN RECEPTORS

In angiotensin system the compound angiotensin II, causes vasoconstriction by acting on a specific receptor known as AT1 receptor. During the studies on angiotensin II physiology the researchers also identified another angiotensin receptor known as AT2 receptor. The research trials to discover ARBs therapy, resulted in bindings of ARB on a part from AT1, also bind AT2 receptors. Many experimental research studies were conducted on animals by drugs which stimulated AT2 receptors. Activation of AT2 receptors resulted in modest vasodilatory and antiproliferative effects. But still no important effect has been reported in human beings by stimulation of AT2 receptors. Another interesting pharmacological effect of surmountability of AT1 was receptor was observed only with AT1 receptor antagonists but not with AT2 receptors. There are many ARBs in treatment of essential hypertension but Candesartan Cilexetil is the only compound that has been found with insurmountable blockade [75].

### 2.8 CANDESARTAN CILEXETIL

After the discovery of ARB in managing high blood pressure large number of angiotensin receptor blockers has been introduced in market for the treatment of essential hypertension.
Among all ARBs agents Candesartan Cilexetil has a unique characteristic of being a long acting which binds AT1 receptor tightly and dissociates slowly. However, efficacy wise it has been reported as to be one of more effective ARB in hypertensive treatment protocols. Candesartan Cilexetil is a pro-drug; it is completely converted to its active compound Candesartan after oral absorption. This drug decreases both types of blood pressure over the 24 hours time interval. Various research projects have suggested that once-daily dose of (16) mg provides a clinically relevant decrease in blood pressure in essential hypertensive patients [76].

Candesartan Cilexetil has been compared with losartan a prototype drug in ARB family and been reported better in regard of its efficacy and tolerability. Reno-protective effects of this drug have also been observed in comparison with losartan. Another reason of being preferred to losartan is its insurmountable blockade of AT1 receptor in comparison to losartan. As once daily monotherapy, Candesartan Cilexetil 16mg is as effective as enalapril 10-20mg, Amlodipine 5mg or Hydrochlorothiazide 25mg, and Candesartan Cilexetil 16mg is more effective than losartan 50mg [77].

The side effects of this drug have been observed of less significance. The safety and tolerability effects were reported nearly same as that of placebo in controlled clinical trials [78]. This drug has been preferred over ACE inhibitors as this does not produce dry cough which is common in ACE inhibitors [79]. This drug in a dosage of 16 mg/day has been reported as effective as lisinopril 20 mg daily for hypertensive type 2 diabetic patients for decreasing blood pressure and micro-albimunuria [80]. The chemical structure of Candesartan Cilexetil has been shown in Figure 2.11.

![Figure 2.11: Chemical structure of Candesartan Cilexetil](image)

1-[[Cyclohexyloxy] carbonyl] oxy) ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)-4biphenyl] methyl]-1H-benzimidazole-7-carboxylate.
Increased serum insulin due to a neoplastic condition or because of insulin resistance may progress in the genesis of high blood pressure, derangement in serum lipids along with alteration in coronary artery disease [81].

This antihypertensive agent is licensed for the treatment of hypertension. In a large scale multicentre research study comprised of 1482 hypertensive patients Candesartan decreased significant reduction in hypertensive patients in comparison with placebo [82]. Various clinical controlled trial projects have indicated that Candesartan Cilexetil appears to be well tolerated by patients. The common observed side-effect that has been mentioned is; headache 4%, respiratory problems 3%, pain in back 2%, vertigo and dizziness in 2%, and nausea reported in 1% of patients. There was no significant change was observed between placebo and Candesartan treatment [83]. As it is difficult to treat severe hypertension with a single drug so a combination has been recommended to control blood pressure within normal ranges. Various research studies have suggested that the antihypertensive monotherapy generally controls blood pressure in about 50-70 percentages of patients [84].

The reductions of endpoints in type-2 diabetics with the angiotensin antagonist Candesartan demonstrated Reno protective effects patients in type-2 diabetics [85]. Candesartan when prescribed with other antihypertensive drugs no significant change was reported with hydrochlorothiazide, nifedipine, digoxin and oral contraceptives in healthy volunteers [86]. In hypertensive patients when this drug was given in combination with hydrochlorothiazide both drugs found effective in treatment protocols [87]).

Results of clinical studies also indicate that Candesartan compared to other angiotensin II receptor blockers (valsartan or losartan) and ACE-inhibitors (e.g. enalapril) has more pronounced efficacy to regulate and maintain blood pressure over 24-48 hour after administration of drug [88].

A variation has been reported in literature regarding the angiotensin receptor antagonist in efficacy wise in hypertension clinical randomized trials [89]. As Candesartan and losartan both
belongs to ARB family but differs in their binding site in at1 receptor at cellular levels [90]. The treatment of severe hypertension is often difficult, and multiple agents are often required. Studies suggest that the antihypertensive monotherapy generally controls blood pressure in about 50-70 percentage of patients [91].

Candesartan is a selective long-acting angiotensin II type1 receptor antagonist. The drug is administered orally [92]. Angiotension II antagonists have been found to decrease blood pressure as effective as angiotension converting enzyme inhibitors. Candesartan is a selective long acting angiotension II type1 receptor antagonist. The drug is administered orally and rapidly absorbed from gastrointestinal tract. Double-blind controlled research studies indicated well toleration and effectiveness of this drug in patients with mild-to-moderate essential hypertension [93].
AIMS AND OBJECTIVES

High blood pressure has been reported as an important determinant risk factor for public health issues regarding cardiovascular system related problems. It incurred a lot of medical and economic constraints globally. As literature survey indicates that the sideeffects are a major problem in normal conventional therapy in the treatment of high blood pressure disease therefore, herbal medicine may be an alternative option in this regard [94].

3.1 Aim
The present study is aimed to compare the effects of herbal medicine as an alternate therapy in comparison to standard allopathic medication in a randomized control trial to observe its efficacy and safety for the management of essential hypertensive patients.

3.2 Objectives / Purpose of study
1. To accurately diagnose hypertension, to improve blood pressure control with Unani or herbal as well as allopathic treatment in order to comparatively determine the efficacy of test and control drugs.

2. To observe and compare the changes of test drug (HypoEss) and control drug (Candesartan) on lipid profile of study subjects.

3. To observe the reported side-effects of test group and control groups of treatment in essential hypertensive patients.

4. To evaluate and report comparison on renal function of both test drug and control drug in study population.

5. To perform blood pressure screening program in the urban and rural setting in Karachi.

6. To examine and repeat blood pressure measurement in case of elevated systolic and/or diastolic readings and to determine the prevalence of essential hypertension as in the mega metropolitan city of Pakistan like, Karachi.

7. To treat and follow up essential hypertensive patients with herbal coded formulations, and their comparison with standard conventional allopathic therapy.

8. The diagnosis and initial evaluation will include blood pressure measurements, history and physical examination, laboratory tests and diagnostic procedures (eg. Complete Blood Count, Urine D/R, Lipid Profile, Blood glucose, Kidney Function Test: BUN/Urea/Creatinine, Liver Function Test: ALT/AST/bilirubin, Alkaline Phosphatase, Treatment management will be focused on lifestyle modification, such as stress reduction, dietary changes, and tobacco avoidance.

9. Drug therapy as indicated will include the coded unani or herbal formulations, proprietary products of herbal manufacturing organization and there in comparison with authentic allopathic medication.
10. The analysis will be based on statistical parameters eg. Reduction in blood pressure, treatment cost and side effects of all forms of medications as utilized in this research study.
METHODOLOGY

This is a comparative, multicentre, prospective, evidence based assessment research work conducted at department of pharmacology & therapeutics Hamdard College of Medicine & Dentistry, Hamdard University, Karachi, Pakistan on patients residing in the urban populace of city of Karachi and its suburbs.

4.1 PHYSICAL EXAMINATION OF STUDY PATIENTS
Selection criteria of male and female patients aged 25-70 years with essential hypertension with sitting DBP≥ 90mm Hg and SBP ≥140mm Hg were included in this study.

Test group: The test group patients were prescribed unani formulation (HypoEss) which comprised of four herbal active ingredients.

Control group: The control group patients were administered allopathic drug Candesartan Cilexetil (16 mg).

4.2 DIAGNOSIS AND INITIAL EVALUATION
The patients included a group of newly diagnosed as well as patients with mild to moderate essential hypertension but not received any treatment. The diagnosis of essential hypertension was established by detecting elevated blood pressure more than 140/90 mm Hg by sphygmomanometer measurement on three different occasions within two weeks. The
possibility that patients had secondary causes of hypertension was excluded by clinical examination.

1. Recording of blood pressure at home, office and working conditions.
2. Previous history and patient’s physical examination.
3. To assess laboratory diagnostic test to detect (serum potassium, blood glucose, serum urea/creatinine, calcium, urinalysis, lipid profile, and liver functions tests).
4. Further diagnostic procedures may be opted to rule out secondary causes.
5. For a confirm diagnosis several readings be taken to label an individual as hypertensive patient.
6. Careful calibration of the BP monitor and thorough patient education are essential if home BP monitoring is used.
7. In case proper home blood pressure recoding facility is not available than consider ambulatory BP monitoring to confirm the diagnosis for newly suspected hypertensive patients.

4.3 INCLUSION CRITERIA
The cases suffering from mild to moderate hypertension were selected on the following lines.

• Patients of 25 to 70 years age group.
• Patient who were of no any pathological findings on routine examination.
• Patients living in Karachi and its adjacent localities, Pakistan.
• All socio-economical classes including lower, middle and upper.

4.4 EXCLUSION CRITERIA

• Patient already diagnosed as diabetic and suffering from diabetic nephropathy.
• Patient already suffering from liver and kidney impairment.
• Patient belonging to area outside Karachi because of inherent difficulty in follow up.
• Pregnant women.
• Patients suffering from cardiac disease.
• Patients having heart known heart problem
• Heart failure
• Failure of kidneys and diagnosed problem of Cerebrovascular accidents were excluded from the study.
4.5 SAMPLE SIZE
Sample size estimation in this clinical study has been done based on general physical examination, general appearance of the patients, age, sex, and local examination of the blood pressure measurement in a pilot study at Amna herbal medical centre North Karachi, Jinnah Post-Graduate Medical Centre medical OPD and medical outpatient department of civil hospital, Karachi. This pilot study includes 200 cases each administered with herbal as test and allopathic medicine as control drug.

4.6 SAMPLE SELECTION
The sample was selected from the outpatient enrolled in Amna herbal medical centre North Karachi, Pakistan, JPMC medical OPD and medical outpatient department of civil hospital, Karachi. On the basis of preliminary clinical examination the patients who were suffering from blood pressure, were referred to the principal investigator of research project and upon the basis of inclusion and exclusion criteria the patient selected as candidate for pilot study.

4.7 DATA COLLECTION
Data collected for this study included filling Performa through personal interview, personal observation, case records, files and documents. The clinical trial Performa attached here which specifies the clinical feature and information.

4.8 STUDY LIMITATIONS
The data was adjusted based on the number of cases in the light of demographic factor using statistical methods like multinomial logistic regression. The data were composed in separate group. The groups were compared after random selection of subject in equal proportion using SPSS software. The subject were divided into two groups the case and the control groups. Finally comparing case and control groups separately

4.9 STATISTICAL ANALYSIS
The statistical analysis is done by Mr. Jawad Baig Mirza, senior statistician and faculty member of Institute of Aero-space University of Karachi, Pakistan. With the help of excel software students’ test was applied for paired data. Interquartile range test was used to show the normal distribution of data. One way ANOVA and Wilcoxon rank sum test were applied to further reinforce the results. Level of significance was set with p-value of less than 0.05.

One Way ANOVA Test

ANOVA (Analysis of variance) has been implicated an important aspect of statistical validity in the disciplines of research and science. It reflects the differences between group’s means when
more than two groups are involved in a research trial. It provides a statistical test to integrate differences among means of several groups in order to see their significance in magnitude of its response.

**Wilcoxon Rank Sum Test**

The Wilcoxon rank sum test basically is a non-parametric tool applied to observe two related samples, matched samples or repeated measurements on a single sample to evaluate their rank difference. It could be applied as an alternative option to paired student’s t-test.

**Interquartile Range**

This statistical tool provides the statistical dispersion of data, being equal to the difference between the upper and lower quartiles. It may also be reflected as first quartile subtracted from 3rd quartile. It evaluates the distribution of data whether or not normally distributed.

### 4.10 ETHICAL ISSUES

Ethical committee clearance and permission was obtained whenever necessary considering:

a) Informing each participant of the study and interviewing and examining the patient who consented to participate in the study.

b) Identity will not be revealed and the data would be kept strictly confidential.

One hundred patients (aged 25-75 years) were randomized to receive HypoEss comprised of *(Dorema ammoniacum (Daroonaj Aqrabi) =3g, Nepeta hindostana (badranj boya) =3g, Rauwolfia serpentina (Asrol) =2g, and Bombyx mori (Abresham) =2g)* in the double-blind, parallel group trial. The patients received 500mg capsule, two capsules twice a day for three month. Selection of doses was on the basis of our clinical practice and doses were adjusted whenever necessary.

### 4.11 HERBAL DRUG FORMULATION

1. Stems of *Dorema ammoniacum*, leaves and stem of *Nepeta hindostana*; root and leaves of *Rauwolfia serpentina* and extract of *Bombyx mori* was used for drug preparation.

2. All the ingredients were washed with potassium permagnate (KMnO4) solution in order to clean them from microorganisms like fungi, Bacteria, virus and also dust particle.

3. After washing with KMnO4 all the herbs were dried.
4. Dried items were then ground separately in a stainless steel grinder at 80 meshes for 15 minutes then mixed thoroughly.

5. Grinded herbal powder was then mixed with 15% glucose solution which was used as binding material.

6. Granules were made after passing through No. 2 size meshwork.

7. 2% Gum acacia + 0.5% magnesium + 1% talcum powder was added as a lubricant source.

8. These granules were then put into a tablet machine and 500 mg tablets were formed.

9. In this process Hydroxyl-propyl-methyl-cellulose (HPMC) was used as a coating agent.

10. Hardness test was applied with 8Lbs pressure to check the hardness of the tablet.

11. Disintegration of the tablet was checked by tablet disintegration machine for 10 minutes.

12. Dissolution of the tablet was assessed by dissolution test machine for 15 minutes.

13. Lastly, the recommended size capsules/tablets were prepared for subjects of clinical research study.

4.12 MATERIALS

1. Tablet (Advant 16 mg) Candesartan, Getz Pharma.

2. Coded Herbal medicine (Table-500mg).


5. Analyzers (selectra-II vital Lab Germany).

6. Disposable syringes.

7. Stationary items.
4.13 DETERMINATION OF SERUM TOTAL CHOLESTEROL

Serum cholesterol was estimated by the enzymatic colorimetric method using kit cat No.303110090 by Eli Tech diagnostic France.

Principle

Cholesterol content of the serum forms a colored complex by means of coupled reactions described below, which was measured by spectrophotometer.

$$\text{Cholesterol esterase}$$

$$\text{Cholesterol ester} + \text{H}_2\text{O} \rightarrow \text{Cholesterol} + \text{Fatty acids}$$

$$\text{Cholesterol oxidase}$$

$$\text{Cholesterol} + \text{O}_2 \rightarrow 4\text{ cholesterol-ozone} + \text{H}_2\text{O}_2$$

$$\text{Peroxidase}$$

$$2\text{H}_2\text{O} = \text{PHENOL} + 4\text{-Amino antipyrine} \rightarrow \text{Red quinone} + 4\text{H}_2\text{O}$$

Calculation

$$\frac{\text{OD sample}}{\text{Cholesterol (mg/dl)}} = \frac{\text{X standard concentration}}{\text{OD standard}}$$

4.14 DETERMINATION OF SERUM TRIGLYCERIDES

Triglycerides were estimated by the enzymatic colorimetric method using kit cat No. 304710050 by Eli Tech Diagnostics France.

Principle

The triglycerides are enzymatically hydrolyzed to glycerol and free fatty acids. The glycerol liberated reacts with glycerokinase and glycerol-3-phosphatase oxidase yielding $\text{H}_2\text{O}_2$, according to following reactions.

$$\text{Lipoprotein lipase}$$
Triglycerides + H₂O → Glycerol + fatty acids

Glycerol kinase

Glycerol + ATP → Glycerol-3-phosphate + ADP

Glycerol-3-P-oxidase

Glycerol-3-phosphate + O₂ → Dihydroxyacetone P + H₂O₂

H₂O₂ + 4 - Amino antipyrine + ADP → Red quinone + 4 H₂O

Calculation

\[ \text{OD sample} \]
\[ \text{Triglycerides (mg/dl)} = \frac{X \text{ standard concentration}}{\text{OD standard}} \]

4.15 DETERMINATION OF SERUM HDL-CHOLESTEROL

Serum HDL-cholesterol was estimated by using kit cat No. 303210040 by Eli Tech Diagnostics France.

Principle

Chylomicrons, very low density lipoproteins (VLDL) and low density lipoproteins (LDL) of serum are precipitated by phospho-tangstic acid and magnesium ions. After centrifuging, high density lipoproteins (HDL) are in the supernatant, cholesterol included in this phase, is increased by enzymatic method.

Calculation

\[ \text{HDL-cholesterol (mg/dl)} = 324 \times \text{OD of sample} \]

4.16 DETERMINATION OF LDL-CHOLESTEROL

LDL-cholesterol was calculated according to friedwald’s Formula, using kit cat No: 114992, 001 (1.14830, ovol).

Calculation

\[ \text{LDL-cholesterol (mg/dl)} = \frac{\text{total cholesterol}}{\text{Triglycerides-HDL}} \]
4.17 DETERMINATION OF SERUM CREATININE

Estimation of serum creatinine without deproteinization according to Jaffé method by using creatinine estimation Cat no. 117119990314 prepared by DiaSys, Diagnostic systems GmbH, Germany.

Principle

Creatinine reacts with picric acid present in alkaline solution and forms a yellow orange compound. In this method low concentration of picric acid is present so proteins cannot be precipitated. Creatinine concentration is measured by the concentration of the dye stuff formed over a certain reaction time. Creatinine and picric acid reacts rapidly with each other therefore secondary reactions do not interfere with the results. The method has high specificity.

Creatinine + Picric acid \[ \rightarrow \text{Creatinine picrate complex} \]

4.18 DETERMINATION OF UREA

Serum urea is estimated by “Urease-GLDH” enzymatic UV test. Cat # 131019990314, DiaSys, Diagnostic systems GmbH, Germany.

Principle:

Urea is reacted enzymatically according to the following equation

\[
\text{Urea} + 2\text{H}_2\text{O} \xrightarrow{\text{Urease}} 2\text{NH}_4 + 2\text{HCO}_3^{-} \\
\text{2- Oxoglutarate} + \text{NH}_4^+ + \text{NADH} \xrightarrow{\text{GLDH}} \text{L-glutaminate} + \text{NAD} + \text{H}_2\text{O}
\]

The decrease in NADH absorbance per unit time is proportional to urea concentration.

GLDH: glutamate dehydrogenase
CHAPTER V

RESULTS

This research study was conducted as an observational clinical evaluation in which an attempt was made to explore the essential hypertension patients with herbal and allopathic medicines to assess their efficacy and safety. All this data was analyzed statistically and the level of significance was applied. A comparative evaluation was conducted of HypoEss with Candesartan Cilexetil. In order to validate the results and observe impact of both test and control drugs (200) essential hypertensive patients screened and enrolled at Amna herbal medical centre, medical OPD of Jinnah Post Graduate Centre and Medical OPD of Civil hospital Karachi, Pakistan, On patients residing in the urban populace and adjoining areas of metropolitan mega city of Karachi.

The intent-to-treat a total population of (200) patients with coded herbal formulation HypoEss, and Candesartan (100) patients by each drug group respectively. The data was collected from January 2013 to February 2014. The collected data of 100 patients of each group; the gender and mean age distribution of patients has been given in table 5.1 and
5.2 and figure 5.1 and 5.2 respectively.

**Table 5.1:** Gender distribution of study participants

<table>
<thead>
<tr>
<th>DRUG GROUP</th>
<th>GENDER</th>
<th>NO. OF PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPOESS (Test drug)</td>
<td>Male</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>100</td>
</tr>
<tr>
<td>CANDESARTAN (Control drug)</td>
<td>Male</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>100</td>
</tr>
</tbody>
</table>

**Figure 5.1:** Gender distribution of study participants.

**Table 5.2:** Distribution of Age Group in Total Patients.
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Treatment Group</th>
<th>Total (n)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test (n)*</td>
<td>Control (n)*</td>
</tr>
<tr>
<td>25 – 35 Years</td>
<td>09</td>
<td>8</td>
</tr>
<tr>
<td>36 – 45 Years</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>46 – 50 Years</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>51 – 60 Years</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>61 – 70 Years</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>71 – 75 Years</td>
<td>06</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

(n)* = number of patients.
Figure 5.2: Distribution of age groups in study participants.

Key:

- HypoEss (test drug),
- Candesartan (control drug)

The normality of the data is represented in IQR plots. Superiority of Allopathic mode of treatment over herbal therapy (see figure 5.3) is evident in inter-drug treatment IQR plots with regard to systolic and diastolic blood pressure while herbal therapy shows beneficial results in triglyceride levels and LDL-cholesterol.
Table 5.3 and figure 5.4 shows the variation in the levels of systolic blood pressure for the patients treated with HypoEss and Candesartan at day 0, day 45 and day 90. Both drug groups HypoEss and Candesartan reduced the mean systolic blood pressure. In HypoEss group patients the mean systolic blood pressure decreased from 161.5± 9.14 mmHg on day 0 to 149.8 ± 6.47 mmHg on day 45 and 137 ± 6.11 mmHg on day 90. However, the mean systolic blood pressure in case of group on day 0 was 162.45 ± 8.60 mmHg which decreased to 139.5 ± 11.94 mmHg on day 45 and to 129.05 ± 6.92 mmHg on day 90. This decrease in systolic blood pressure was observed as statistically highly significant (p <0.001) when compared between day 0, 45 and 90 in both drug groups. The average percentage decrease in systolic blood pressure was observed as 15.17 percent from day 0 to day 90 in test group while; a 20.56 percent reduction in systolic blood pressure was observed in case of control group patients.

Table 5.3: Changes in systolic blood pressure from day 0, 45 and 90 of treatment with HypoEss and Candesartan in patients with essential hypertension.
<table>
<thead>
<tr>
<th>GROUPS</th>
<th>DAY 0</th>
<th>DAY 45</th>
<th>DAY 90</th>
<th>P – value</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D 0–45</td>
<td>D 45–90</td>
<td>D 0–90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HypoEss</td>
<td>161.5 ± 9.14</td>
<td>149.8 ± 6.47</td>
<td>137 ± 6.11</td>
<td>t = 16.13 p &lt; 0.001</td>
<td>t = 18.85 p &lt; 0.001</td>
</tr>
<tr>
<td>Candesartan</td>
<td>162.45 ± 8.60</td>
<td>139.5 ± 11.94</td>
<td>129.05 ± 6.92</td>
<td>t = 13.7 p &lt; 0.001</td>
<td>t = 8.11 p &lt; 0.001</td>
</tr>
<tr>
<td>Candesartan vs. HypoEss</td>
<td>t = -7.58 p &lt; 0.001</td>
<td>t = -8.62 p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key:

HypoEss (test drug),
Candesartan (control drug),
Figures are in (Mean ± SEM),
All observations were measured in mmHg,
□ Indicates decrease in percentage.
Figure 5.4: Changes in systolic blood pressure from day 0, 45, and 90, of treatment with HypoEss and Candesartan in patients with essential hypertension.

Key:

HypoEss: test drug
Candesartan: control drug
Blood pressure in mmHg.

Table 5.4 and figure 5.5 shows the variation in the levels of diastolic blood pressure for the patients treated with HypoEss and Candesartan at day 0, day 45 and day 90. Both HypoEss and Candesartan reduced the diastolic blood pressure. The mean diastolic blood pressure of patients of HypoEss group decreased from 94.1 ± 11.31 mmHg on day 0 to 85.9 ± 8.74 mmHg on day 45 and 77.1 ± 6.12 mmHg on day 90. This reduction was statistically highly significant with a (P
<0.001) when compared between day 0 to day 45, between day 45 to day 90 and between day 0 to day 90. The average percentage reduction was 18.07 percent from day 0 to day 90. The mean diastolic blood pressure of Candesartan group patients was 103.7 ± 8.63 on day 0, which reduced to 89.25 ± 7.76 mmHg on day 45 and to 81.25 ± 7.05 mmHg on day 90. This decrease in diastolic blood pressure was statistically highly significant (P <0.001) when compared between day 0 and day 45, between day 45 to day 90 and between day 0 to day 90. The average percentage decrease in diastolic blood pressure was 21.65 percent from day 0 to day 90 in case of control drug group.

Table 5.4: Changes in mean diastolic blood pressure from day 0, 45, 90, of treatment with HypoEss and Candesartan in patients with essential hypertension.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>DAY 0</th>
<th>DAY 45</th>
<th>DAY 90</th>
<th>P − value</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D 0−45</td>
<td>D 45−90</td>
</tr>
<tr>
<td>HypoEss</td>
<td>94.1 ± 11.31</td>
<td>85.9 ± 8.74</td>
<td>77.1 ± 6.12</td>
<td>t = 17.7 p &lt; 0.001</td>
<td>t = 17.32 p &lt; 0.001</td>
</tr>
<tr>
<td>Candesartan</td>
<td>103.7 ± 8.63</td>
<td>89.25 ± 7.76</td>
<td>81.25 ± 7.05</td>
<td>t = 13.07 p &lt; 0.001</td>
<td>t = 17.58 p &lt; 0.001</td>
</tr>
<tr>
<td>Candesartan vs. HypoEss</td>
<td>t = 2.86 p=0.0046</td>
<td>t = 4.45 p &lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key:
HypoEss (test drug),
Candesartan (control drug),
Figures are in (Mean ± SEM),
All observations were measured in mmHg.
□ Indicates decrease in percentage.
Figure 5.5: Changes in diastolic blood pressure from day 0, 45, and 90, of treatment with HypoEss and Candesartan in patients with essential hypertension.

Key:

HypoEss: test drug
Candesartan: control drug
Blood pressure in mmHg.

Table 5.5 and figure 5.6 show the changes in the levels of serum total cholesterol for the patients treated with HypoEss and Candesartan at day 0, day 45 and day 90. The mean serum total cholesterol of HypoEss group was observed as 173.27 ± 18.47 mg/dl on day 0 to 174.21 ± 15.18 mg/dl on day 45 and to 173.04 ± 15.58 6mg/dl on day 90. There was no pronounced effect on serum total cholesterol was observed from day 0 to day 45 and day 90 in case of test drug
group. Statistically the calculated value of p was observed as non-significant. The percentage change of serum total cholesterol was observed as 0.13 % from day 0 to day 90. Patients of Candesartan group also showed no significant changes in serum cholesterol levels. Mean serum total cholesterol was 176.43 ± 19.72 mg/dl on day 0 and it was decreased to 174.84 ± 16.61 mg/dl on day 45 and remained 176.53 ± 15.29 mg/dl on day 90. This effect or response was found statistically nonsignificant when compared between days 0 to day 90. The average percentage increase was found 0.06 % from day 0 to day 90.

Table 5.5: Changes in total cholesterol from day 0, 45, and 90 of treatment with HypoEss and Candesartan in patients with essential hypertension.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>DAY 0</th>
<th>DAY 45</th>
<th>DAY 90</th>
<th>P - value</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>D 0−45</td>
<td>D 45−90</td>
<td>D 0−90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HypoEss</td>
<td>173.27 ± 18.47</td>
<td>174.21 ± 15.18</td>
<td>173.04 ± 15.58</td>
<td>t = -1.7, p=0.09</td>
<td>↓ 0.13</td>
</tr>
<tr>
<td>Candesartan</td>
<td>176.43 ± 19.72</td>
<td>174.84 ± 16.61</td>
<td>176.53 ± 15.29</td>
<td>t = 2.65, p=0.0095</td>
<td>↑ 0.06</td>
</tr>
<tr>
<td>Candesartan vs. HypoEss</td>
<td>t = 0.28, p=0.78</td>
<td>t = 1.6, p=0.11</td>
<td>t = 0.13</td>
<td>t = 0.18</td>
<td></td>
</tr>
</tbody>
</table>

Key:
HypoEss (test drug),
Candesartan (control drug),
Figures are in (Mean ± SEM),
All observations were measured in mg/dl,
□ Indicates decrease in mg/dl.
↑ Indicates increase in mg/dl.
Figure 5.6: Changes in mean total cholesterol from day 0, 45, day 45 and 90 of treatment with HypoEss and, Candesartan in patients with essential hypertension.

Key:

HypoEss: test drug
Candesartan: control drug

Serum cholesterol in mg/dl.

Table 5.6 and figure 5.7 reflects the mean serum triglyceride level of HypoEss group was observed 120.74 ± 16.29 mg/dl at day 0 which was decreased to 119.14 ± 14.82 mg/dl at day 45
and a further reduction was noticed as 118.44 ± 15.54 mg/dl at day 90. This decrease was found significant with (P < 0.001) when compared between day 0 to day 90. The percentile change from day 0 to day 90 was observed as 1.90 percent. However the changes of Candesartan group were observed as 123.78 ± 19.6mg/dl on day 0 and 124.48 ± 18.74 mg/dl on day 45. On day 90 values of serum triglycerides was noted as 123.63 ± mg/dl. The average reduction was found no significant when compared between day 0 to day 45, between day 45 to day 90 and between day 0 to day 90. The percentage change from day 0 to day 90 was observed as 0.12 percent.

**Table 5.6:** Changes in mean serum triglyceride from day 0, 45, and 90 of treatment with HypoEss and Candesartan in patients with essential hypertension.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>DAY 0</th>
<th>DAY 45</th>
<th>DAY 90</th>
<th>P − value</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D 0−45</td>
<td>D 45−90</td>
</tr>
<tr>
<td>HypoEss</td>
<td>120.74 ± 16.29</td>
<td>119.14 ± 14.82</td>
<td>118.44 ± 15.54</td>
<td>t = 3.12 p=0.0024</td>
<td>t = 1.27 p=0.21</td>
</tr>
<tr>
<td>Candesartan</td>
<td>123.78 ± 19.16</td>
<td>124.48 ± 18.74</td>
<td>123.63 ± 17.01</td>
<td>t = -1.24 p=0.22</td>
<td>t = 1.07 p=0.29</td>
</tr>
<tr>
<td>Candesartan vs. HypoEss</td>
<td>t = 2.234 p=0.027</td>
<td>t = 2.25 p=0.025</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key:
HypoEss (test drug),
Candesartan (control drug)
Figures are in (Mean ± SEM),
All observations were measured in mg/dl,
□ Indicates decrease in mg/dl.
Figure 5.7: Changes in serum triglycerides from day 0, 45, and 90 of treatment with HypoEss and Candesartan in patients with essential hypertension.

Key:

HypoEss: test drug
Candesartan: control drug
Serum triglyceride in mg/dl.

Table 5.7 and figure 5.8 shows the mean LDL cholesterol level of HypoEss group patients the serum LDL cholesterol level was recorded as $114.1 \pm 12.36$ mg/dl at day 0 and it was decreased to $111 \pm 10.27$ mg/dl at day 45 a further reduction in serum LDL cholesterol level was observed
on day 90 of study period as its value was observed as 108.3 ± 8.41 mg/d. When compared statistically between day 0 to day 45 and day 45 to day 90 the change were found significant with a (p<0.001). A percentage change of 5.8% was observed from day 0 to day 90 of study. However, in case of Candesartan patients the serum LDL-C level was found as 114.16 ± 15.5 mg/dl and at day 45 the level of serum LDL cholesterol was recorded as 113.9 ± 13.21 mg/dl. No significant change was found between day 0 and day 90 as the values of serum LDL was observed as 113.61 ± 12.21 mg/dl on day 90. This response was found as non significant when compared between day 0 and day 90. The percentage reduction from day 0 to day 90 was observed as 0.48 percent.

**Table 5.7:** Changes in mean LDL-C level from day 0, 45, and 90 of treatment with HypoEss and Candesartan in patients with essential hypertension.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>DAY 0</th>
<th>DAY 45</th>
<th>DAY 90</th>
<th>P − value</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D 0−45</td>
<td>D 45−90</td>
</tr>
<tr>
<td>HypoEss</td>
<td>114.1 ± 12.36</td>
<td>111 ± 10.27</td>
<td>108.3 ± 8.41</td>
<td>t = 5.94 p &lt; 0.001</td>
<td>t = 6.13 p &lt; 0.001</td>
</tr>
<tr>
<td>Candesartan</td>
<td>114.6 ± 15.15</td>
<td>113.9 ± 13.21</td>
<td>113.61 ± 12.21</td>
<td>t = 0.54 p = 0.6</td>
<td>t = 0.55 p = 0.6</td>
</tr>
<tr>
<td>Candesartan vs. HypoEss</td>
<td>t = 1.733 p = 0.08</td>
<td></td>
<td>t = 3.58 p &lt; 0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key:

HypoEss (test drug),
Candesartan (control drug),

Figures are in (Mean ± SEM), All observations were measured in mg/dl,

☑ Indicates decrease in mg/dl.
Figure 5.8: Changes in mean LDL-C level from day 0, 45, and 90, of treatment with HypoEss and Candesartan in patients with essential hypertension.

Key:

HypoEss: test drug  
Candesartan: control drug  
Serum LDL-C in mg/dl.

Table 5.8 and figure 5.9 reflects the mean HDL cholesterol of HypoEss group patients.
On day 0, mean serum HDL-C was recorded as 40.37 ± 3.28 mg/dl which was noted as 40.5 ± 2.48 mg/dl on day 45 and was observed as 39.87 ± 2.00 mg/dl on day 90. When compared between days 0 to day 45, and day 45 to day 90 of study this decrease was found statistically non-significant. The percentage change in HDL cholesterol from day to day 90 was recorded as 1.24 percent. While in case of Candesartan group the HDL-C value on day 0 was noted as 42.96 ± 5.93 mg/dl and at day 45 it was decreased to 41.77 ± 4.97 mg/dl and a further reduction was observed on day 90; as it was observed as 40.37 ± 4.24 mg/dl. When statistically compared between days 0 to 45, day 45 to day 90 a significant (p<0.001). The percentage change from day 0 to day 90 was observed as 6.03 percent.

**Table 5.8:** Changes in mean serum HDL-C level from day 0, 45, and 90 of treatment with HypoEss and Candesartan in patients with essential hypertension.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Day 0</th>
<th>Day 45</th>
<th>Day 90</th>
<th>P - value</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D 0−45</td>
<td>D 45−90</td>
</tr>
<tr>
<td>HypoEss</td>
<td>40.37 ± 3.28</td>
<td>40.5 ± 2.48</td>
<td>39.87 ± 2.00</td>
<td>t = -0.54</td>
<td>p=0.59</td>
</tr>
<tr>
<td></td>
<td>t = 2.43</td>
<td>p=0.017</td>
<td>t = 1.5</td>
<td>p=0.14</td>
<td>↓1.24</td>
</tr>
<tr>
<td>Candesartan</td>
<td>42.96 ± 5.93</td>
<td>41.77 ± 4.97</td>
<td>40.37 ± 4.24</td>
<td>t = 3.75 p &lt; 0.001</td>
<td>t = 4.26 p &lt; 0.001</td>
</tr>
<tr>
<td>Candesartan vs. HypoEss</td>
<td></td>
<td></td>
<td></td>
<td>t = 2.3 p=0.02</td>
<td>t = 1.07 p=0.29</td>
</tr>
</tbody>
</table>

Key:
HypoEss (test drug),
Candesartan (control drug),
Figures are in (Mean ± SEM),
All observations were measured in mg/dl,
Indicates decrease in mg/dl.

**Figure 5.9:** Changes in mean serum HDL-C level from day 0, 45 and 90 of treatment with HypoEss and Candesartan in patients with essential hypertension.

Key:
- HypoEss: test drug
- Candesartan: control drug
- Serum HDL-C in mg/dl.
Table 5.9 and figure 5.10 shows the mean serum urea level of HypoEss group on day 0 the serum urea was observed as 20.13 ± 1.55 mg/dl which was noted as to 19.87 ± 1.26 mg/dl on day 45 and it was found increased on day 90 and recorded as 20.17 ± 1.45 mg/dl. When compared between days 0 to day 45, and day 90 this effect was observed as statistically non-significant. The percentage change in serum urea level from day 0 to day 90 was recorded as 0.20 percent. In Candesartan group on day 0 serum urea was observed as 20.27 ± 1.92 mg/dl and at day 45 its level was observed as 19.73 ± 1.55 and day 90 was found as 20.05 ± 1.45 mg/dl. When compared between days 0 to 45 and 90 the effect was found non-significant. The percentage change from day 0 to day 90 was observed as 1.09 percent.

Table 5.9: Changes in serum urea level from day 0, 45, and 90 of treatment HypoEss and Candesartan in patients with essential hypertension.

<table>
<thead>
<tr>
<th>GROUPS</th>
<th>DAY 0</th>
<th>DAY 45</th>
<th>DAY 90</th>
<th>P − value</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>D 0−45</td>
<td>D 45−90</td>
</tr>
<tr>
<td>HypoEss</td>
<td>20.13</td>
<td>19.87</td>
<td>20.17</td>
<td>t = 1.76 p = 0.08</td>
<td>t = -1.9 p = 0.059</td>
</tr>
<tr>
<td></td>
<td>1.55</td>
<td>1.26</td>
<td>1.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>20.27</td>
<td>19.73</td>
<td>20.05</td>
<td>t = 3.9 p &lt; 0.001</td>
<td>t = -2.23 p &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>1.92</td>
<td>1.55</td>
<td>1.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan vs. HypoEss</td>
<td>t = -0.7 p = 0.48</td>
<td>t = -0.59 p = 0.56</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key:
HypoEss (test drug),
Candesartan (control drug),
Figures are in (Mean ± SEM),

All observations were measured in mg/dl,

☐ Indicates decrease in mg/dl.

↑ Indicates increase in mg/dl.

Figure 5.10: Changes in serum urea level from day 0, 45, and 90 of treatment with HypoEss and Candesartan in patients with essential hypertension.

Key:

HypoEss: test drug

Candesartan: control drug

Serum urea in mg/dl.
Table 5.10 and figure 5.11 reflects the mean serum creatinine level of HypoEss group was 0.55 ± 0.14 mg/dl on day 0 which was increased to 0.57 ± 0.15 mg/dl on day 45 and on day 90 it slightly decreased to 0.56 ± 0.11 mg/dl. When compared statistically between day 0 to day 90; P was observed as non-significant. The percentage change in serum creatinine level from day 0 to day 90 was 1.82 percent. In Candesartan group on day 0 the serum creatinine was observed as 0.57 ± 0.15 mg/dl and at day 45 its value was observed as 0.56 ± 0.10 mg/dl and again on day 90 the creatinine level was noted as 0.55 mg/dl ± 0.10 mg/dl. When compared statistically between days 0, 45 and 90 this response was seen as significant. The percentage change from day 0 to day 90 was observed as 3.51 percent.

**Table 5.10:** Changes in serum creatinine level from day 0, 45, and 90 of treatment with HypoEss and Candesartan in patients with essential hypertension.

<table>
<thead>
<tr>
<th></th>
<th>DAY 0</th>
<th>DAY 45</th>
<th>DAY 90</th>
<th>P – value</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>P – value</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>D 0-45</td>
<td>D 45-90</td>
<td>D 0-90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HypoEss</td>
<td>0.55 ± 0.14</td>
<td>0.57 ± 0.15</td>
<td>0.56 ± 0.11</td>
<td><strong>t = -1.18</strong></td>
<td>↑ 1.82</td>
</tr>
<tr>
<td></td>
<td>p = 0.24</td>
<td>p = 0.414</td>
<td>p = 0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>0.57 ± 0.15</td>
<td>0.56 ± 0.10</td>
<td>0.55 ± 0.10</td>
<td><strong>t = 0.75</strong></td>
<td>↓ 3.51</td>
</tr>
<tr>
<td></td>
<td>p = 0.48</td>
<td>p = 0.63</td>
<td>p = 0.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Candesartan vs. HypoEss</td>
<td></td>
<td></td>
<td><strong>t = -0.47</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p = 0.64</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>t = -0.14</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p = 0.88</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Key:

HypoEss (test drug),

Candesartan (control drug),

Figures are in (Mean ± SEM),

All observations were measured in mg/dl,

□ Indicates decrease in mg/dl.

↑ Indicates increase in mg/dl.
Figure 5.11: Changes in serum creatinine level from day 0, 45, and 90 of treatment with HypoEss and Candesartan in patients with essential hypertension.

Key:

HypoEss: test drug  Candesartan: control drug  Serum creatinine in mg/dl.
The F-value generated by applying One Way ANOVA test for SBP, DBP, TGs and LDL Cholesterol further reinforces our finding of having significant difference amongst the treatments (see Table 5.11). Moreover, if we pair the subjects in Wilcoxon Rank Sum test for the above mentioned parameters, the outcome stands significant (see Table 5.12).

**Table 5.11: Results of One Way ANOVA Test (Allopathic Vs Herbal Treatment)**

<table>
<thead>
<tr>
<th></th>
<th>SBP</th>
<th>DBP</th>
<th>TGs</th>
<th>Cholesterol</th>
<th>LDL-Cholesterol</th>
<th>HDL-Cholesterol</th>
<th>S.U</th>
<th>S.C</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-value</td>
<td>74.18</td>
<td>19.76</td>
<td>5.07</td>
<td>2.56</td>
<td>12.83</td>
<td>1.135</td>
<td>0.344</td>
<td>0.02</td>
</tr>
<tr>
<td>P-value</td>
<td>2.2e-15</td>
<td>1.5e-05</td>
<td>0.025</td>
<td>0.11</td>
<td>4.3e-04</td>
<td>0.29</td>
<td>0.56</td>
<td>0.885</td>
</tr>
</tbody>
</table>

**Table 5.12: Results of Wilcoxon Rank Sum Test (Allopathic Vs Herbal Treatment)**

<table>
<thead>
<tr>
<th></th>
<th>SBP</th>
<th>DBP</th>
<th>TGs</th>
<th>Cholesterol</th>
<th>LDL-Cholesterol</th>
<th>HDL-Cholesterol</th>
<th>S.U</th>
<th>S.C</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-value</td>
<td>4.5e15</td>
<td>1.9e-05</td>
<td>0.0225</td>
<td>0.146</td>
<td>0.003</td>
<td>0.765</td>
<td>0.813</td>
<td>0.575</td>
</tr>
<tr>
<td>Accept(0) / Reject(1)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
The table 5.11 reflects the undesired effects of study drugs in essential hypertensive patients. All of above side effects have been observed during study duration or being reported by the patients. There were no significant difference were observed in test drug in comparison to standard control drug.

**Table: 5.13** Observed and patients reported adverse effects during study period from day 0 to day 90.

<table>
<thead>
<tr>
<th>SIDE-EFFECTS</th>
<th>CONTROL DRUG</th>
<th>TEST DRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>0</td>
<td>02</td>
</tr>
<tr>
<td>Headache</td>
<td>02</td>
<td>01</td>
</tr>
<tr>
<td>Lethargy</td>
<td>0</td>
<td>02</td>
</tr>
<tr>
<td>Weakness</td>
<td>01</td>
<td>01</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>01</td>
<td>02</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>01</td>
<td>02</td>
</tr>
<tr>
<td>Backache</td>
<td>01</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>02</td>
<td>0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>0</td>
<td>01</td>
</tr>
<tr>
<td>Total Patients</td>
<td>08</td>
<td>11</td>
</tr>
</tbody>
</table>

**Key:**
- HypoEss (test drug),
- Candesartan (control drug)
CHAPTER – VI

DISCUSSION
DISCUSSION

High blood pressure is no doubt a disease with great financial and social consequences affected all population irrespective of any discretion of gender and nation. It is the main cause of progression of cardiovascular disease worldwide. It increased the incidence of stroke, coronary artery disease and problems of cardiac failure globally. Instead of progress in medical sciences the prevalence of hypertension does not decreased accordingly.

In present study we have and compared the effects of standard allopathic drug Candesartan Cilexetil as control and coded-herbal formulation (HypoEss) as test drug in essential hypertensive patients. The angiotensin II receptor blockers (ARBs) represent a newer class of antihypertensive agents [95]. Candesartan is indicated for the treatment of high blood pressure and cardiac failure [96, 97]. Several clinical and basic research studies with Candesartan in healthy volunteers and diagnosed essential hypertensive patients have reported a significant and long lasting decrease in both systolic and diastolic blood pressure. This study demonstrates significant changes in blood pressure with both Candesartan and HypoEss.

In the present study it was found that Candesartan and HypoEss significantly reduced both systolic and diastolic blood pressure. Candesartan reduced the mean systolic blood pressure from 162.45 mmHg on day 0 to 129.05 mmHg on day 90 with a percentage decrease of 20.56% percent. Whereas, reduced the mean systolic blood pressure from 161.5 mmHg on day 0 to 137 mmHg on day 90 with a percent reduction of 15.17%, when compared the mean systolic blood pressure between day 0 to day 90; showing a highly significant (P <0.001) statistically for both drug groups.

Both drug groups have also decreased mean diastolic blood pressure significantly as reflected in result tables and figures. In case of control group the mean diastolic blood pressure reduced from 103.7 mmHg on day 0 to 81.25 on day 90th of study period with a percentage reduction of 21.65%. While in case of test group the mean diastolic blood pressure decreased from 94.1 mmHg to 77.1 mmHg on day 90th of study duration with a percentage reduction of 18.07%. When compared the mean diastolic blood pressure between day 0 to day 90; showing a highly significant (P <0.001) statistically for both the drugs. The results of our present study are in accordance with [98] who have reported a reduction of 19% in systolic blood pressure and 17.75% in case of diastolic blood pressure after 12 weeks of Candesartan Cilexetil treatment in hypertensive patients.
The results of present study may also be correlated with the results of research clinical trial of [99] who have observed a reduction of 19% in systolic blood pressure and 18% decrease in mean diastolic blood pressure with Candesartan Cilexetil 4 weeks treatment. Similarly [100] reported a decrease of 15 mmHg in case of systolic blood pressure and a decrease of 5-10 mm Hg in mean diastolic blood pressure with a significant (p<0.001) after 8 days treatment, the clinical research study of [101] also found a decrease of 10.8 mmHg in systolic blood pressure and 7.3 mmHg in mean diastolic blood pressure with a significant p (<0.001) after 6 weeks of Candesartan treatment.

The research findings of researchers like [102, 103] differ from our findings in regard of decrease in percentage and magnitude of response; this may be because of difference in drug dosage and duration of study. The decrease of systolic and diastolic blood pressure with test group patients have also been reported and found in literature with research studies of [104,105,106,107]. As test medicine was a combination formula of different herbal compounds so its cumulative effect in literature have not been reported as whole effect but as a single compound the effects of this coded herbal formulation has been reported and documented by various researchers in their findings. The antihypertensive effect of herbal medicine has also been reported by [108, 109, and 110] in their studies.

The effect of angiotensin II receptor blocker Candesartan Cilexetil on lipid metabolism in essential hypertensive patients have also been observed in present study. The findings of this study revealed that Candesartan Cilexetil has decreased serum HDL-C in study patients but serum TG, TC and LDL-C were not affected much by this medication.

The effects of present study and findings of other authors revealed that Candesartan may be indicated inessential hypertensive patients with respect to lipid derangements. In our findings of control patients a decrease in serum HDL-C level has been observed which decreased from 42.96 mg/dl on day 0 to 40.37 mg/dl on day 90th of study duration. The levels of TG, TC, and LDL-C remained unaffected by this drug. This decrease in HDL-C level has been found significant in our results.

This effect on HDL-C levels in present study may also be correlated with the research findings of [111] as they have also reported a decrease in serum HDL-C at the completion of their with treatment of Candesartan Cilexetil. The other aspect which relates our findings are a non-significant change in the levels of TG, TC, and LDL-C with Candesartan treatment is also in accordance with the results of [112].

The changes produced in lipid metabolism of test group patients reflect the effects of a combination treatment of (HypoEss). The hypolipidemic effect of herbal ingredients has been reported by various authors in their research works. As we have introduced a combination preparation of four herbal active
compounds in essential hypertensive patients hence, their magnitude of response reflects their cumulative effect. The results of test group on serum lipids may be correlated with study conducted by [113] other authors like [114] and [115] have also reported hypolipidemic effects of herbal plants in their research outcomes. However the research findings of [116] and [117] differ from our findings and this may be because of combination of four herbal ingredients in our study.

The effects of angiotension II receptor blockers, Candesartan on serum urea and creatinine of control patients was found decreased from 1.09 % to 3.51% respectively as reflected in result tables and figure. This effect of Candesartan may be found in accordance to studies conducted by [118] who have reported renoprotective effects of angiotension II type-1receptor antagonists Candesartan by improving proteinuria and creatinine clearance in case of end-stage Renal Disease (ESRD) patients.

Similarly another research clinical trial conducted by [119], observed a beneficial effect of angiotension II receptor blockers Candesartan Cilexetil by blockade of rennin angiotensin system (RAS) may slow down the progression of renal impairment by improving proteinuria, serum urea and creatinine. Reduction in albulmunuria and blood pressure are short-term treatment goals for subsequent stabilization of renal function. Some other authors like [120], and [121] have also reported renoprotective effects of Candesartan on renal performance in case of renal impairment in context to improvement in urea and creatinine levels in hypertensive and diabetic hypertensive patients with nephropathy.

The result of present study in case of serum urea of test patients did not affected much. The serum urea level in case of HypoEss increased slightly with a percentile change of 0.20 % which reflected a non-significant response statistically from day 0 today 90th of present study. While; in case of serum urea of Candesartan group found changed slightly from base line readings with a cumulative percentile change of a decrease of 1.09 % from day 0 to day 90th of study. This also reflects a non-significant change from day 0 to day 90 of treatment duration. The observations of serum creatinine of HypoEss was observed as increased from 0.55 mg/dl on day 0 to 0.56 mg/dl on day 90th of study reflected an increase of 1.82 % from day 0 to day 90 of clinical trial duration. The changing effects of serum creatinine in test group treatment observations reflected a non-significant response in study subjects, while; the effects of Candesartan were of nonsignificance in control patients.

The basic aim and objective of our present study was to determine the efficacy of HypoEss in essential hypertension as to decrease blood pressure in case of systolic and diastolic blood pressure. This effect was found statistically significant and observed a significant decrease in systolic and diastolic blood pressure of test group patients in comparison to standard allopathic drug which is already included in treatment protocols. The test drug results also reflected beneficial effects in lipid metabolism of hypertensive patients with regard to control drug. The changes on Serum urea creatinine were observed as non-significant by test drug in comparison to control drug Candesartan Cilexetil. This may reflects an
altered response of herbal treatment which did not deranged kidney functions in comparison to Candesartan Cilexetil.

CHAPTER – VII

CONCLUSION
CONCLUSION

In present study, we have observed the comparative effects of Candesartan Cilexetil with coded unani medicine HypoEss in essential hypertensive patients. Our main objective was to evaluate the antihypertensive effect of coded herbal medicine with a standard established allopathic medicine. We have observed a 15.17% reduction in mean systolic blood pressure while, 18.07% decrease was observed in case of diastolic blood pressure.

This effect on blood pressure was observed statistically highly significant.

Our other objective in this study was to compare the effects of both drug groups on lipid metabolism of study patients. We have observed that the herbal compound has been reported with beneficial effects on serum triglycerides and serum LDL-Cholesterol. This beneficial lipidemic effect was found significant statistically. However, the effect of herbal formulation on serum urea and creatinine was found unaffected statistically. This effect might be helpful in renal hypertensive patients for their treatment.

The results of present study may be helpful in the treatment of essential hypertension particularly in those patients who are reluctant to receive allopathic treatment. This beneficial effect of herbal formulation may be applied in patients of hyper triglyceridemia and hyperlipidaemia due to different reasons. This herbal combination treatment may be beneficial for hypertensive patients suffering from Hyperlipidaemia and prefer unani medicine in comparison to allopathic mode of treatment. However, dosage adjustment may be suggested for impaired renal patients suffering from essential hypertension. The effectiveness of alternative treatment has been observed in comparison to allopathic drug while; herbal treatment is cost-effective in comparison to allopathic drug.
HYPERTENSION: FUTURE PROSPECTS

The disease of high blood pressure is an important aspect of public health issue worldwide both in developed countries in general and economically developing countries in particular. A large proportion of the population across the globe is affected from the disease but ignorant or unaware of their condition. On the other hand patients who are diagnosed but having no effective treatment at their access. Strategies are required at administrative as well on professional basis as to prevent the disease at its earliest stages and effective treatment be made available for patients without any discrimination across the world.

Collective efforts are required at national and international levels as to find out more safe and cost-effective alternative treatment options to make treatment accessible for all hypertensive patients at their community levels. Long-term multicentre randomized control trials shall be conducted as to develop new, safe and effective drugs with maximum efficacy and cost-effectiveness for population across the globe. Efforts shall be made to make drug accessible for all patients without the discrimination of age, sex race and nation.
REFERENCES
REFERENCES

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APPENDICES APPENDIX - I

CLINICAL TRIAL PROTOCOL FOR THE MANAGEMENT OF ESSENTIAL HYPERTENSIVE PATIENTS

Department of Pharmacology & Therapeutics
Hamdard College of Medicine & Dentistry
Hamdard University, Karachi

PATIENTS EVALUATION RECORD

Patient ID: _____________ Reg No: _______________ Date:

_________________________ Patient’s Name

_________________________ S/O, W/O: ____________________________________

Age: ______________ Sex: _______________ Occupation: ______________________

Marital Status____________________________________________________________

Address: __________________________________________________________________

Presenting Complains: _______________________________________________________

Previous Medications:________________________________________________________

Family History: _____________________________________________________________

Drug History: _______________________________________________________________

Patient Consent: _____________________________________________________________
PHYSICAL AND GENERAL EXAMINATION

CVS: _________________  Pulse: _________________  B.P: _________________

BMI: ______________________________________________________________

Respiratory System:_______________________________________________________

G.I.T:___________________________________________________________________

C.N.S: __________________________________________________________________

Others: ________________________________________________________________

OBSERVATION OF CLINICAL TRIAL PARAMETERS FROM (DAY-0 TO DAY-90)

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>DAY-0</th>
<th>DAY-15</th>
<th>DAY-30</th>
<th>DAY-45</th>
<th>DAY-60</th>
<th>DAY-75</th>
<th>DAY-90</th>
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<tr>
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<tr>
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<td></td>
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<tr>
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</tr>
<tr>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Serum LDL</td>
<td></td>
<td></td>
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<tr>
<td>Serum Urea</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Serum Creatinine</td>
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<td></td>
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</tbody>
</table>
Drug prescribed to patient:

Herbal: -------- -- yes / No
Allopathic: -------- yes / No

APPENDIX - II CONSENT FORM

Department of Pharmacology & Therapeutics
Hamdard College of Medicine & Dentistry
Hamdard University, Karachi

I, hereby give my consent to a treatment given to me. The nature and extent of such treatment or procedure, I have entirely to the discretion of the Medical Officer performing the above said purpose will not hold of the Hospital staff responsible for any risk involved in or incident occurring during or after the treatment or procedure.

Signature: _______________________________

Date: ___________________________________

Address: _______________________________