# COMPARATIVE EFFECT OF ANTIHYPERTENSIVE DRUGS (LISINOPRIL AND AMLODIPINE) WITH MORINGA OLEIFERA LEAF EXTRACT ON SOME LIVER ENZYMES

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**Abstract** - Drug related liver disorders have been the most important form of liver disease in the last decade. This is due to the negligence and alarming increase in drug abuse and also due to the toxic effects of inadequate therapies employed in the treatment of various diseases. With regards to this, this research aimed at using Moringa oleifera leaf extract to achieve hepatoprotective activity in Dexamethasone-salt induced hypertension in albino wister rats using liver enzymes as biomarkers; and to compare the effect with the conventional drugs (Lisinopril and Amlodipine). A total of 30 albino wister rats were divided into six groups with 5 animals in each group. Group 1 served as the negative control (Un-induced), Group 2 served as the positive control (Induced but not treated) while Groups 3, 4, 5 and 6 were the test groups (Induced and treated with conventional drugs and graded concentrations of Moringa oleifera (leaf extract). All the groups were fed ad libitum with standard diet and water throughout the three weeks experimental period. Blood samples were collected and the serum was used to measure the levels of liver enzymes (ALP, ALT and AST) using COBAS C311 auto analyzer. Data obtained were analyzed using the statistical package for social sciences (SPSS) version 27.0. There was nostatisticalsignificant difference (P>0.05) in the levels of serum ALP, ALT and AST between albino wister rats exposed to the conventional drugs. There was also no statistical difference in the levels of serum ALP, ALT and AST between albino wister rats exposed to the low and high dose of the extract. There was also no statisticalsignificant difference in the levels of serum ALP, ALT and AST between albino wister rats exposed to a combination of the conventional drugs and the low dose of the extract. Based on these results, it can be concluded that Moringa oleifera leaf extract could be used in combination with conventional drugs for the treatment and management of liver diseases and hypertension.

**Keywords** - Comparative, Lisinopril, Amplodipine, Moringa Leaf Extract, and Liver Enzymes.

## I. INTRODUCTION

Hypertension is a prevalent condition worldwide and a major risk factor for cardiovascular disease (Ferguson et al., 2018). It is a condition in which the force of the blood against the walls of artery is too high, usually defined as blood pressure above 140/90mmHg and considered severe when the pressure is above 180/120mmHg. Stroke and ischemic heart disease are increasingly doubling mortality rates (Lewington et al., 2022). One of the main reasons for this may be the higher prevalence of hypertension in men than in women (Hajjar et al., 2016). Predisposing factors to hypertention include elevated average blood pressure, excessive drinking and smoking other than at meal (Kloner and Rezkalla, 2017).

The antihypertensive drug “Lisinopril” has been classified as an angiotensin converting enzyme (ACE) inhibitor, frequently used in the treatment of hypertension and other related conditions such as heart failure, myocardial infarction and diabetic nephropathy. Lisinopril differs from other antihypertensive drugs by having a long half-life, it is hydrophilic, and it is not broken down by the liver (Chen et al., 2018).

Amlodipine is widely used in the management of hypertension. It belongs to a class of drugs known as Calcium Channel Blockers (CCBs) Amlodipine is a dihydropyridine calcium channel blocker (CCB) which reduces the blood pressure by inhibiting the entry of calcium through the L-channels into the cardiac and vascular smooth muscle cells and thus blocking their contractile effects. (Unger et al., 2020). Herbal medicine from medicinal plants since time immemorial has been used to treat different infections (Ali et al., 2022). The advantage of using medicinal plants for treatment of different disease is due to their les side effect, high potency, less patient toxicity, affordability and ecofriendly (Ali et al., 2022).

Moringaoleifera is a tree that grows widely in many tropical and subtropical countries. It belongs to the family Moringaceae with a single genus family and 13 known species (Khawaja etal., 2010). It is known as the drumstick tree, the horseradish tree, and the ben oil tree (Razisetal., 2014). Almost all the parts of this plant have been used for various ailments including the treatment of inflammation, hypertension and infectious diseases along with cardiovascular, gastrointestinal, hematological and hepatorenal disorders (Becker et al., 2003).

The liver normal color is brown and the external surface is smooth. The liver is about 2% of body weight in the adult,which amounts to approximately 1400g in females and 1800g in males. The liver receives its blood supply from two sources: 80% is from the portal vein, which drains the spleen and intestines. The remaining 20%, the oxygenated blood,

is from the hepatic artery (Garcia and Bosch, 2010).The liver is considered the largest gland in the body, it performs various functions of digestion, blood purification, and also detoxifies various drugs (Bahodirov, 2005).

The cells in the liver contain proteins called enzymes that facilitate chemical reactions. When liver cells are damaged, the enzymes in the cells leak out into the blood where they can be measured by blood tests. Liver enzymes are important in the assessment of hepatocellular injury and they form a major component for the investigation of liver function. Enzymes found in the liver are specific for certain reaction.

The transaminases; Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) are useful in the early diagnosis of liver disorders. Very high levels are seen in extensive acute hepatic necrosis such as severe viral hepatitis.

Alcoholic liver disease and cirrhosis are associated with mild to moderate elevation of transaminases. (Carl et al., 2008; Harsh, 2010).

Lisinopril and Amlodipine are frequently used as monotherapies to manage hypertension. These two antihypertensive agents have different, complementary modes of action to reduce blood pressure, making them suitable for combination therapy (Gottwald et al., 2017). The problem is that Lisinopril can cause harm to the body because it is not metabolized by the liver and goes into circulation without being detoxified (Oyedeji et al., 2018).

Also, amlodipine does not undergo first past effect by the liver (Meredith and Elliot,1992). Although, the two drugs have prescribed dose of administration, hepatotoxicity has been reported with antihypertensive drugs use (Dharmendar, 2015). Herbal medicines are usually taken with unknown dose, therefore, this study is to compare the dosage effect of Lisinopril, Amlodipine with Moringaoleifera leaf extract on the levels of liver enzymes.

Moringaoleifera is medicinal in nature and has been used in traditional medicine. Despite its medicinal value, there are no recommended doses for its usage. This study therefore is geared towards comparing the dosage effect of the antihypertensive drugs (Lisinopril and Amlodipine) with Moringaoleifera leaf extract so as to ascertain a proper dose that can effectively manage liver enzymes level for adequate liver function, and also for prevention of complications in hypertensive patients.

## II. MATERIALS AND METHOD

### 2.1. EXPERIMENTAL DESIGN

A total of 30 albino Wister rats was used for this study. The animals were purchased from the animal house, department of Pharmacology, Faculty of Pharmaceutical science, University of Jos, Nigeria. The animals were kept in a cage under normal environmental conditions and fed with standard diet and water ad libitum. The rats were allowed to acclimatize to the laboratory environment for some weeks before commencement of experiment.

The animals were alslocated into control and experimental groups with a total of six (6) groups consisting of five (5) rats each. The weight of each animal was measured with the aid of a weighing scale and the mean weight of each group was taken weekly throughout the study period.

The experiment consisted of two basic periods; the inducement period and the treatment period. The inducement period lasted for a week, in which animals in certain groups were induced with hypertention using 2mg/kg body weight of Dexamethasone-salt and their drinking water was substituted with 4% NaCl.

The treatment period lasted for three (3) weeks, during which animals in certain groups were treated with a combination of 0.07mg per kg body weight of Lisinopril and 0.27mg per kg body weight of Amlodipine, 20mg/kg body weight of Moringa oleifera leaf extract, 40mg/kg of Moringa oleifera leaf extract, and a combination of Lisinopril, Amlodipine and the low dose of Moringa oleifera leaf extract.The grouping is as follows:

Group 1: Consists of albino rats not induced and given just normal saline (Negative control).

Group 2: Consists of dexamethasone salt-induced (given 4% salt solution and dexamethasone) hypertensive albino rats (Positive control).
Group 3: Consists of dexamethasone salt-induced hypertensive albino rats and treated with 0.07mg/kg body weight of Lisinopril and 0.27mg/kg body weight of Amlodipine.
Group 4: Consists of dexamethasone salt-induced hypertensive albino rats and treated with 20mg/kg body weight of Moringa oleifera leaf extract.

Group 5: Consists of dexamethasone salt-induced hypertensive albino rats and treated with 40mg/kg body weight of Moringa oleifera leaf extract.

Group 6: Consists of dexamethasone salt-induced hypertensive albino rats and treated with 0.07mg/kg of Lisinopril, 0.27mg/kg of Amlodipine and 20mg/kg of Moringa oleifera leaf extract.

| Groups | Number of Animals | Treatment Given | Dosage per body weight | Rout of Administration |
|---|---|---|---|---|
| 1 | 5 | Distilled Water | - | Oral |
| 2 | 5 | Dexamethasone-salt | 2mg/kg | Oral |
| | | Sodium chloride | 4% | |
| 3 | 5 | Lisinopril | 0.07mg/kg | Oral |
| | | Amlodipine | 0.27mg/kg | |
| 4 | 5 | *Moringa oleifera* leaf extract | 20mg/kg | Oral |
| 5 | 5 | *Moringa oleifera* leaf extract | 40mg/kg | Oral |
| 6 | 5 | Lisinopril | 0.07mg/kg | Oral |
| | | Amlodipine | 0.27mg/kg | |
| | | *Moringa oleifera* leaf extract | 20mg/kg | |

| Wk/Grp | Wk 1 | Wk 2 | Wk 3 | Wk 4 |
|---|---|---|---|---|
| Grp 1 | 5 | 5 | 5 | 5 |
| Grp 2 | 5 | 5 | 5 | 5 |
| Grp 3 | 4 | 3 | 3 | 3 |
| Grp 4 | 4 | 3 | 3 | 3 |
| Grp 5 | 3 | 3 | 3 | 3 |
| Grp 6 | 5 | 4 | 4 | 3 |

Key: Week = Wk, Group = Grp.

**Table2.1Experimental Design**

| S/N | Drugs/Chemical Used | Dosage (per body weight) | Route of Administration |
|---|---|---|---|
| 1. | Dexamethasone-salt | 2mg/kg | Oral |
| 2. | NaCl | 4% | Oral |
| 3. | Lisinopril | 0.07mg/kg | Oral |
| 4. | Amlodipine | 0.27mg/kg | Oral |
| 5. | Moringa oleifera | 20mg/kg and 40mg/kg | Oral |

**Table 3.2:Drugs/Chemicals Used**

## III. RESULTS AND DISCUSSION

### 3.1. RESULTS INTERPRETATION AND PRESENTATION

Data were analyzed using statistical package for social sciences (SPSS Version 27.0). Descriptive statistics was used to summarize data by finding the mean and standard deviation.

| | | Grp 1 Mean ±SD | Grp 2 Mean ±SD | Grp 3 Mean ±SD | Grp 4 Mean ±SD | Grp 5 Mean ±SD | Grp 6 Mean ±SD |
|---|---|---|---|---|---|---|---|
| ALP | WK 2 | 219.60±98.41 | 237.20±38.26 | 301.33±66.46 | 274.67±77.02 | 281.67±115.14 | 195.25±36.88 |
| | WK 3 | 254.66±104.36 | 218.00±67.03 | 278.33±21.83 | 258.33±69.79 | 317.00±28.62 | 281.50±44.25 |
| | Wk 4 | 298.60±14.08 | 295.80±13.31 | 303.00±4.58 | 388.67±151.93 | 324.67±81.40 | 253.67±59.55 |
| ALT | WK 2 | 58.20±12.14 | 65.78±13.27 | 64.97±0.70 | 80.50±8.70 | 77.43±11.24 | 62.98±15.22 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | WK 3 | 80.88±24.61 | 71.30±19.45 | 59.03±9.18 | 50.33±2.40 | 68.70±14.61 | 73.60±30.63 |
| | WK 4 | 123.32±11.74 | 100.82±18.43 | 142.30±38.96 | 108.47±19.91 | 126.77±40.50 | 112.30±14.84 |
| AST | WK 2 | 183.18±23.37 | 176.96±30.54 | 213.37±53.35 | 178.53±28.21 | 212.83±8.79 | 220.15±24.45 |
| | WK 3 | 295.94±102.99 | 257.90±78.16 | 307.37±103.08 | 215.50±32.64 | 201.03±45.06 | 254.25±66.38 |
| | WK 4 | 263.08±78.87 | 245.46±34.6 | 261.50±52.84 | 213.70±46.30 | 306.93±15.70 | 221.07±50.03 |

Key:Standard Deviation = ±SD, Alkaline Phospahatase = ALP, Alanin Aminotransferase = ALT, Aspartate Aminotransferase = AST, Week = WK, Group = Grp.

**Table3.1: Mean ± Standard Deviation of Serum ALP, ALT and AST of Albino Wister Rats**

Table 4.1 above presents the mean serum ALP, ALT and AST of albino wister rats by groups by weeks after every week (for three weeks).

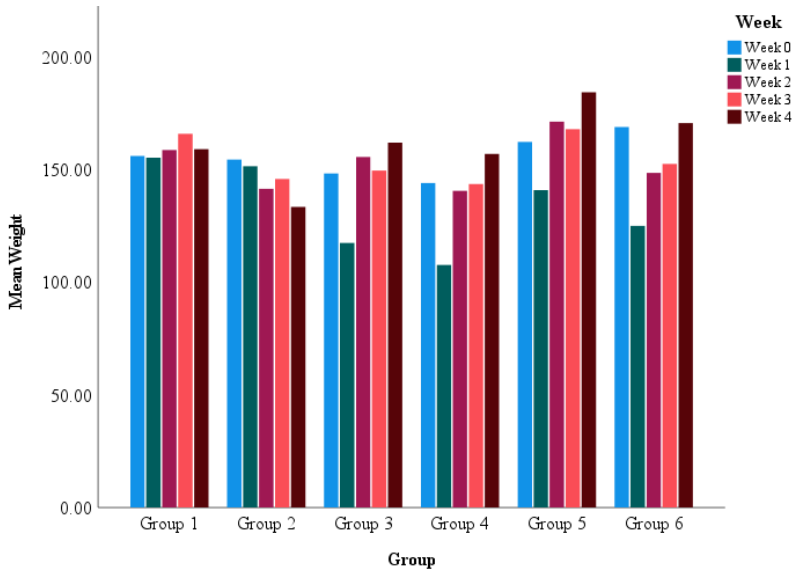


**Figure3.1: Clustered Bar of Mean Weight (g) by Group by Week**

Figure 4.1 above is a bar chart that shows the mean body weight of wistar rats in grams (g) across the experimental groups. In Group 1, the initial mean body weight was 155.8g, 155g in week one, 158.4g in week two, 165.6g in week three and 158.8g in the fourth week of the experiment. In Group 2, the initial mean body weight was 154.2g, 151.2g in the first week, 141.2g in week two, 145.6g in week three and 133.2g in the fourth week of the experiment. In Group 3, the initial mean body weight was 148g, 117.3g in week, 155.3 in week 2, 149.3g in week three and 161.7g in the fourth week experiment. In Group 4, the initial mean body weight was 143.8g, 107.5g in the first week, 140.3g in week two, 143.3g in week three and 156.7g in the fourth week of the experiment. In Group 5, the initial mean body weight was 162g, 140.7g in the first week, 171g in week two, 167.7g in week three and 184g in the fourth week of the experiment. In Group 6, the initial mean body weight was 168.2g, 124.8g in the first week, 148.3g in the second week, 152.3g in the third and 170.3g in the fourth week of the experiment.

## IV. DISCUSSION

Acute toxicity testing was not carried out in this study because a dietary supplement known as Nature's feed high strength Moringa (800mg) was used. Although Moringaoliferaintake is safe at levels < or = 1,000 mg/kg body weight but genotoxic at levels of 3000mg/kg body weight according to George et al. (2012). The dosage used in this study therefore is in agreement with this claim.

Table 4.1 shows the mean and standard deviation of serum ALP, ALT and AST in dexamethasone-salt induced hypertensive albino wister rats. The serum level of ALP, ALT and AST of group 1(negative control = 257.62±83.99, 87.47±32.17 and 247.40±126.46 respectively) when compared with group 2(positive control = 250.33±54.09, 79.30±22.56 and 226.77±60.92 respectively) were found to be higher and statistically insignifant with P-values: 0.78, 0.43 and 0.57 respectively. This finding contradicts that of (Moss, 1997) who stated that the response of the liver to any form of biliary tree obstruction induces the synthesis of liver enzymes by

hepatocytes and that some of the newly formed enzymes goes into circulation to increase enzyme activity in serum.Comparing the level of serum ALP, ALT and AST of group 1(257.62±83.99, 87.47±32.17 and 247.40±126.46 respectively) with group 3(Lisinopril and Amlodipine = 294.22±37.03, 88.77±44.94 and 260.74±75.65 respectively), the levels in group 3 were found to be higher than that of group 1 with insignificant P-values: 0.23, 0.94 and 0.78 respectively. This contradicts the findings of Amacher, etal. (2013) who stated that daily administration of Lisinopril and Amlodipine increases enzyme level. The comparison between group 1(257.62±83.99, 87.47±32.17 and 247.40±126.46) and group 4(low dose of the extract = 255.22±110.69, 79.77±27.45 and 202.58±36.43) shows that the mean serum level of ALP, ALT and AST of group 4 were lower than that of group 1(257.62±83.99, 87.47±32.17 and 247.40±126.46) with P-values 0.23, 0.56 and 0.31 respectively, which is statistically not significant. This result is in agreement with the findings of Carl, et al. (2008) that peak activities of serum aminotransferases and alkaline phosphatase bears no relationship to prognosis and may fall with worsening of the liver disease condition.The mean serum ALP, ALT and AST obtained from group 5(high dose of the extract = 307.78±74.63, 90.97±35.07 and 276.27±55.81 respectively) were higher than that of group 1(257.62±83.99, 87.47±32.17 and 247.40±126.46 respectively) with P-values 0.16, 0.81 and 0.87 respectively. This contradicts the findings of Omar, et al. (2017) and Oluwadara, et al. (2018) that there was no significant difference in the group treated with high dose of the extract.

In the same vain, the level of serum ALP, ALT and AST obtained from group 6(low dose of the extract, Lisinopril and Amlodipine = 242.55±56.95, 80.29±28.98 and 232.8±47.87 respectively) were lower than that of group 1(257.62±83.99, 87.47±32.17 and 247.40±126.46 respectively) with P-values 0.61, 0.56 and 0.72 respectively. This contradicts the findings of Omar, et al. (2017) and Oluwadara, et al. (2018) that there was no significant difference between the group treated with low dose of the extract, Lisinopril and Amlodipine. This is also in agreement with the findings of Cappuccio and Macgregor, (2014) that there was no significant difference between the three drug combination and this may be due to certain component in the extract or drugs that acts as an antagonist.

In figur3.1: rats in group 1 showed a slight decrease in body weight in week 1, which increase in week 2 and 3, and decreases in week 4. Rats in group 2 showed decrease in body weight in week 1 and 2, which increases in week 3 and decreases in week 4. In group 3, there was decrease in week 1, increase in week 2, decrease in week 3 and increase in the fourth week. Group 4 showed a decrease in week 1 with progressive increase across week 2, 3 and 4. Group 5 showed the same pattern when compared to group 3. Group 6 followed the same pattern with group 4. The weight patterns showed that the extract has effect on weight reduction and this is in conformity with the study carried out by Ezat, et al. (2020) who stated that Moringa oleifera leafhas effect in high-fat diet-induced obesity in rats. A study by Raja, et al. (2022) and Buettner, (2007) also supported this claims.

## V. CONCLUSION

This study was a comparison of the effects of the antihypertensive drugs (Lisinopril and Amlodipine) with Moringa oleifera leaf extract on hepatic enzymes of dexamethasone-salt induced hypertensive albino wister rats. The findings revealed that leaf extract of Moringa oleifera improves serum hepatic ALP and ALT level at both low and high concentrations of 20mg/kg body weight and 40mg/kg body weight respectively. However, serum AST level was improved at higher concentration of the extract compared to the lower concentration. Thus, these findings justify the use of Moringa oleifera leaf extract in the treatment of hepatic diseases with abnormal AST levels as a sign of a diseased liver.

## RECOMMENDATIONS

- Further studies should be carried out on the exact component(s) responsible for the mechanism of action of Moringa oleifera leaf extract.
- Adequate and proper awareness on the plant toxicity should be embarked upon in other to curb the menace that comes with drug abuse and misuse.

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