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ORIGINAL ARTICLE

ANTIDIABETIC AND TOXICITY ASSESSMENT OF COMBINATION OF PIPER NIGRUM AND ARTOCARPUS HETROPYLLUS

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Abstract:

The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 285 million in 2010. Based on current trends, the International Diabetes Federation projects that 438 million individuals will have diabetes by the year 2030. However, on chronic usage most of these agents produced several side effects, including hypoglycemic coma, insulin resistance, hyper-sensitivity, cholesterol, jaundice, abdominal pain, anorexia and metallic taste [4]. For various reasons in recent years, the popularity of herbal medicines in diabetic control has increased. Natural plant drugs are frequently considered to be less toxic with lower side effects than synthetic ones [7].Therefore searching herbal product with anti-diabetic activity possessing fewer side effects receives considerable publicity and provides an opportunity to cure this disease.

Keywords: Antidiabetic, Prevalence, Hyperglycaemia, Toxicity, Diabetic Anatomy etc.

INTRODUCTION

The Diabetes Mellitus is being one of five leading causes of deaths and debilitating disease in the world. One hundred and fifty million people were suffering from diabetes wide reaching, which is almost five times more than the estimates one decade ago and it may double in the year 2030 [1]. The development of diabetic complications is a major cause of morbidity and mortality and is an ever-increasing burden to healthcare authorities in both developed and developing nations. Epidemiological studies have confirmed that hyperglycemia is the most important

factor in the onset and progress of diabetic complications [2]. Diabetes mellitus or simply diabetes is a chronic metabolic disorder of carbohydrate, lipid and protein metabolism characterized by hyperglycemia, glycosurea, hyperlipidemia, negative nitrogen balance and sometimes ketonemia due to insufficient or complete cessation of insulin synthesis or secretion and/or peripheral resistance to insulin action [3]. The hallmark of diabetes mellitus is polyuria-excessive urine production**,** polydipsia-excessive thirst and polyphagia- excessive eating [4]. Diabetes is a condition primarily defined by the level of hyperglycaemia giving rise to risk of microvascular damage (retinopathy, nephropathy and neuropathy). It is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular complications, increased risk of macrovascular complications (ischaemic heart disease, stroke and peripheral vascular disease), and diminished quality of life[5]. The pathogenesis of diabetes mellitus and its complications is managed by insulin and oral administration of hypoglycemic drugs such as sulfonylureas and biguanides [6]. However, on chronic usage most of these agents produced several side effects, including hypoglycemic coma, insulin resistance, hyper-sensitivity, cholesterol, jaundice, abdominal pain, anorexia and metallic taste [4]. For various reasons in recent years, the popularity of herbal medicines in diabetic control has increased. Natural plant drugs are frequently considered to be less toxic with lower side effectsthan synthetic ones [7].Therefore searching herbal product with anti diabetic activity possessing fewer side effects receives considerable publicity and provides an opportunity to cure this disease [8].

The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 285 million in 2010. Based on current trends, the International Diabetes Federation projects that 438 million individuals will have diabetes by the year 2030 (Fig.1). Although the prevalence of both type 1 and type 2 DM is increasing worldwide, the prevalence of type 2 DM is rising much more rapidly, presumably because of increasing obesity, reduced activity levels as countries become more industrialized, and the aging of the population. In the most recent estimate for the United States (2010), the Centers for Disease Control and Prevention (CDC) estimated that 25.8 million persons, or 8.3% of the population, had diabetes (27% of the individuals with diabetes were undiagnosed). Approximately 1.6 million individuals (>20 years) were newly diagnosed with diabetes in 2010. DM increases with aging. In 2010, the prevalence of DM in the United Sates was estimated to be 0.2% in individuals aged <20 years and 11.3% in individuals aged >20 years. In individuals aged >65 years, the prevalence of DM was 26.9%. The prevalence is similar in men and women throughout most age ranges (11.8% and 10.8%, respectively, in individuals aged >20 years). Worldwide estimates project that in 2030 the greatest number of individuals with diabetes will be aged 45–64 years. [9]

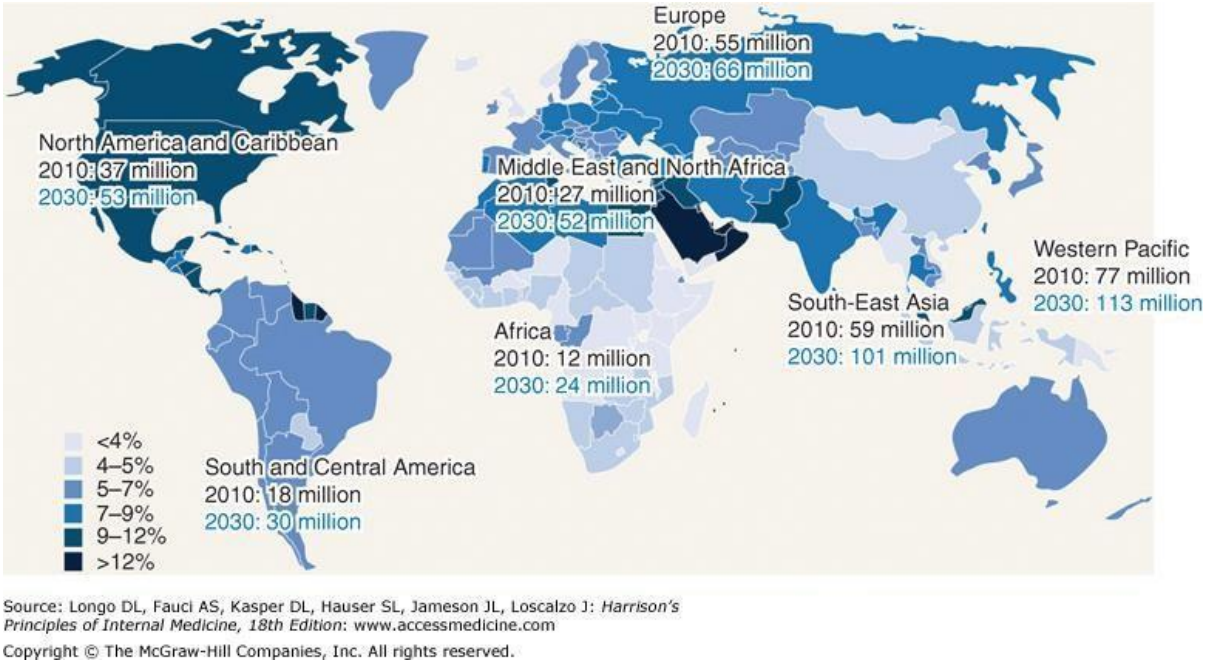


Figure 1:-Worldwide prevalence of diabetes mellitus. Comparative prevalence (%) of estimates of diabetes (20–79 years), 2020

Presently as many as 50% of people with diabetes are undiagnosed. Since therapeutic intervention can reduce complications of the disease, there is a need to detect diabetes early in its course. The risk of developing Type 2 diabetes increases with age, obesity, and lack of physical activity. Its incidence is increasing rapidly, and by 2030 this number is estimated to almost around 552 million [10,11]. Diabetes mellitus occurs throughout the world, but is more common (especially type 2) in the more developed countries, where the majority of patients are aged between 45 and 64 years. The greatest increase in prevalence is, however, expected to occur in Asia and Africa, where most patients will probably be found by 2030 [11] (Table.1). It is projected that the latter will equal or even exceed the former in developing nations, thus culminating in a double burden as a result of the current trend of transition from communicable to non-communicable diseases [12,13]

Extraction Procedure

Figure 2: Assembly extraction Apparatus

RESULTS AND DISCUSSION

Table 1: Soxhlet Extraction of the Plants

Plant	Part Used	Method Of Extraction	Solvents	Weight Of Powder Taken(A	Weight Of Product (B)	Percentage Yield (W/V)
Artocarpus hetrophyllus	leaf	Continuous Hot percolation by Soxhlet apparatus	Ethanol (60-80°C)	**500 gm**	**49.4gm**	**9. 88**
Piper nigrum	leaf	Continuous Hot percolation by Soxhlet apparatus	Ethanol (60-80°C)	**500 gm**	**78.5gm**	**15.7**

A = Weight of powder plant material B = Weight of extract

Percentage yield = (B/A) X 100

DISCUSSION

The Percentage yeld of Artocarpus hetrophyllus = 9. 88 The Percentage yeld of Piper nigrum = 15.7

Ethanolic extract of artocarpus hetrophyllus may contain the following phytochemicals

1. Carbohydrate

2. Flavonoids

3. Proteins and amino acids

4. Glycosides

5. Saponins

6. Tannins

Ethanolic extract of artocar Piper nigrum may contain the following phytochemicals

1. Steroids

2. Flavonoids

3. Alkaloids

4. Saponins

5. Tannins

6. Terpenoids

ACUTE TOXICITY STUDIES

Acute toxicity studies on the albino rats show no morality at a dose of 2000mg/kg, during a time period of 14 days. NOAEL were not seen in the entire study period. This acute study helps to predict that it does not contain any type of toxicity and it is full safe. So 100 mg/kg b.w (1/20th) and 200mg/kg b.w (1/10th) and 400mg/kg (1/5th) were selected of that dose for the further toxicological study.

SUBACUTE TOXICITY STUDIES

In-vivo sub-acute oral toxicity study were performed to evaluate the toxicities of 28

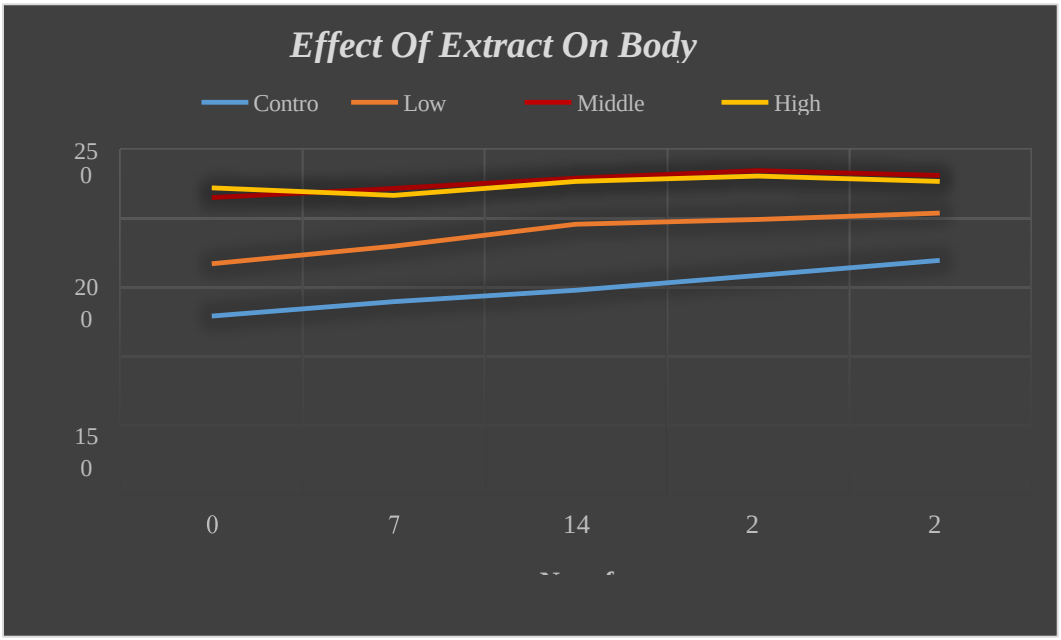
days by continuous administration of the prepared extract , as per the procedure mentioned in the section

Daily observations include changes in skin, fur, eyes, mucus membrane (nasal), respiratory rate, circulatory signs (heart rate), autonomic effects (salivation, lacrimation, perspiration, piloerection, urinary incontinence and defecation), central nervous system (drowsiness, gait, tremors and convulsion), body weight and food consumption. The results were summarized in table 12 to 16. At the end of the treatment, the animals were bled from the retro orbital sinus for clinical pathology assessment which included analysis of various haematology parameters and blood biochemistryparameters. Consequently the animals were sacrificed by cervical dislocation and necropsied to facilitate gross pathological examination of organs.

EFFECT OF EXTRACT ON PERCENTAGE CHANGE IN BODY WEIGHT

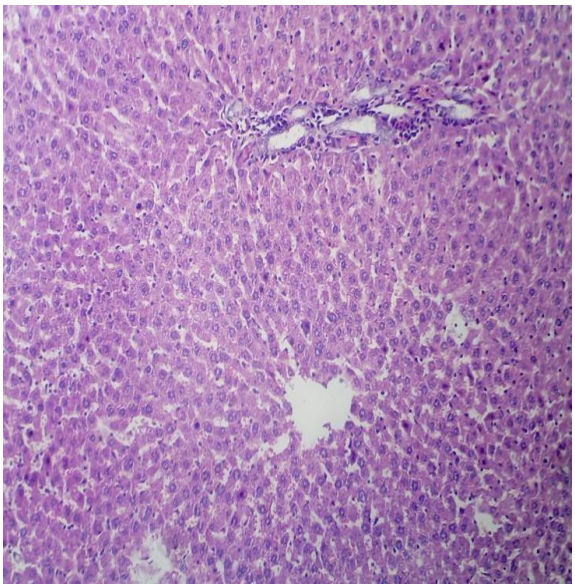
Sex	Dose	Days				
		0	**7**	**14**	**21**	**28**
Male	**Control**	129.4±3.26	139.8±2.3	148.2±2.33	158.8±1.85	169.8±3.15
	Lower Dose	167.5±2.82	180±1.69	196±1.63	199.5±2.07	204±2.70
	Middle dose	215.5±2.35	222±4.31	229.5±0.89	235±1.51	231.5±1.59
	Higher Dose	222.5±4.0	217±2.55	227±2.53	231±2.42	227±1.70
Female	**Control**	123.9±3.20	130±3.92	139.4±3.76	150±5.15	160.2±4.32
	Lower Dose	225±2.92	221±2.43	225±4.2	222±4.16	222±3.26
	Middle dose	**203±2.92**	212±2.43	212±4.2	214±4.16	216±3.26
	Higher Dose	**190±2.27**	203±2.40	208±2.06	211±2.18	215±1.24

FIGURE 3:- EFFECT OF EXTRACT ON BODY WEIGHT

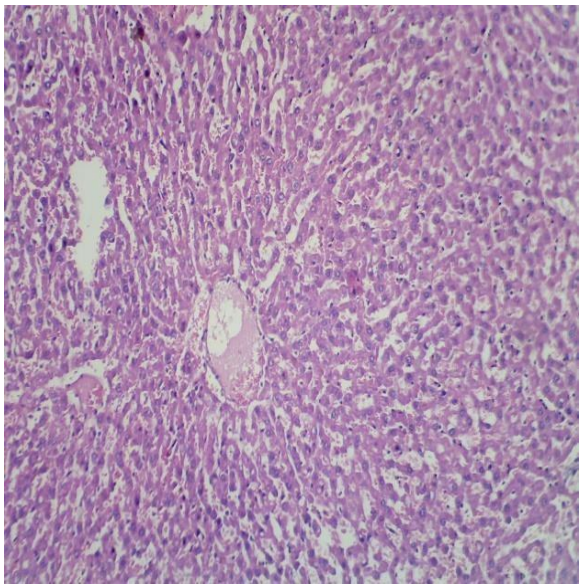


HISTOPATHOLGICAL ASSESSMENT OF EXTRACT

Figure 4:- T.S of Rat Liver Showing Normal Cells in Subacute Toxicity Study of Extract



Control

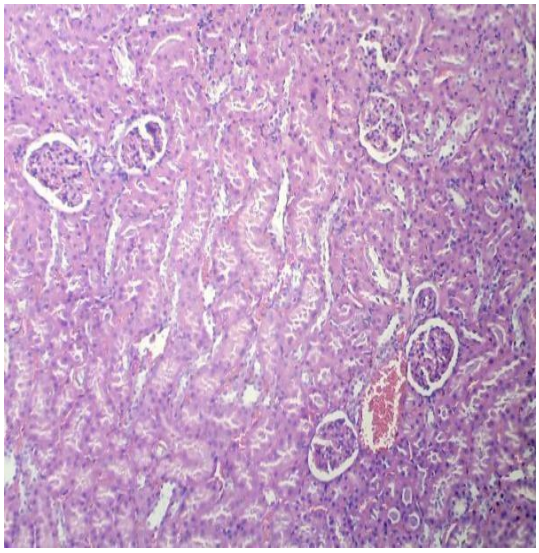


Lower dose

Section studies from the liver shows normal lobular architecture. Individual hepatocyte, central vein and sinusoids shows p- unremarkable. There is no evidence of inflammation and necrosis.

KIDNEY

Figure 5:- T.S of Rat Kidney Showing Normal Cells In Sub Acute Toxicity Studies of Extract



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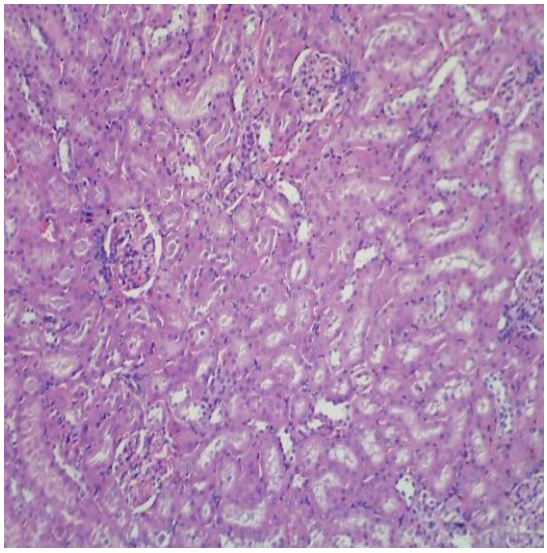
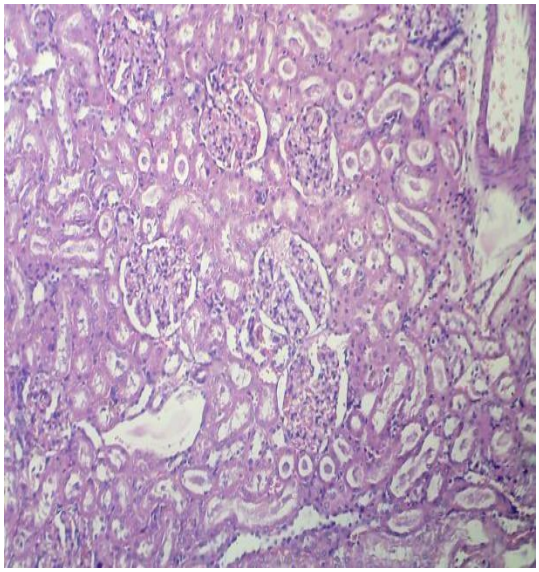
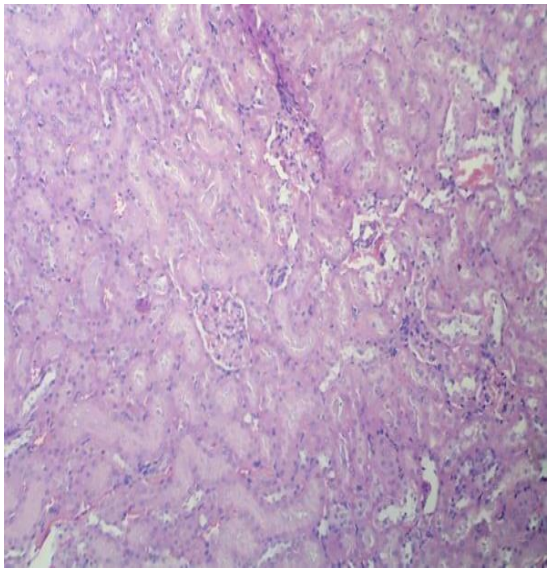


Lower dose



Medium dose



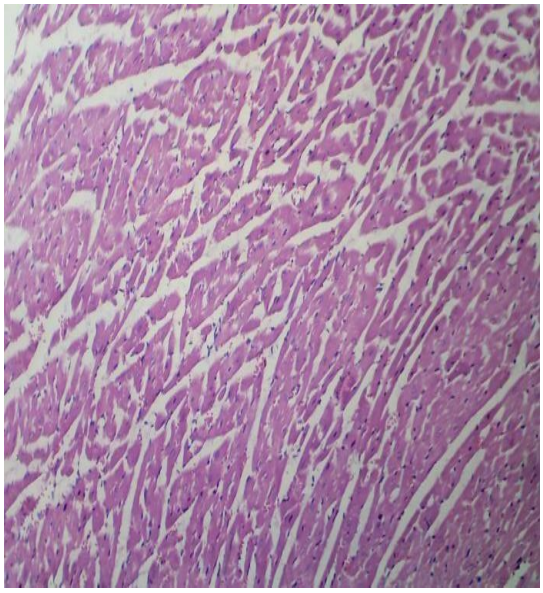
Higher dose

Microscopic appearance

Section studies from the kidney show normal cortex and medulla. The glomeruli, interstitium and blood vessels are unremarkable. There is no evidence of inflammation and necrosis.

HEART

Figure 6:- T.S of Rat Heart Showing Normal Cells In Sub Acute Toxicity Studies of Extract



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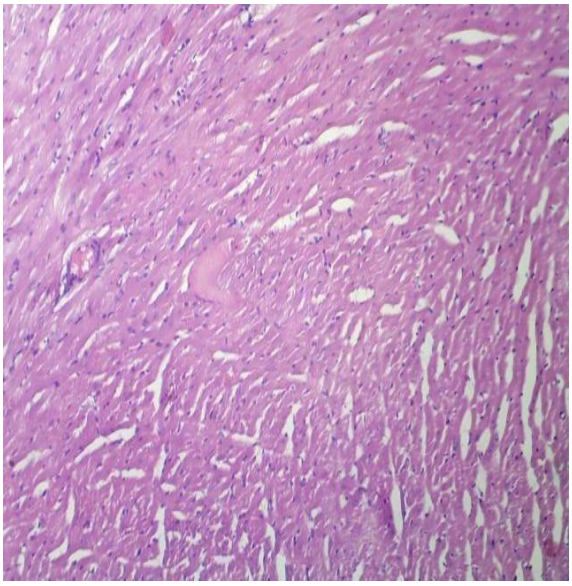

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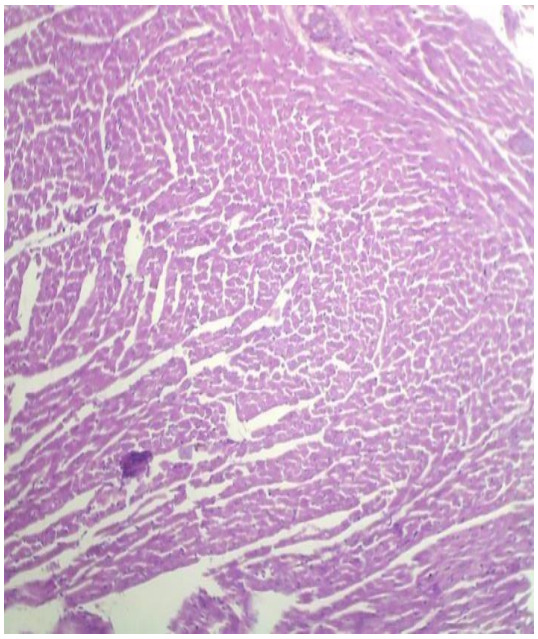

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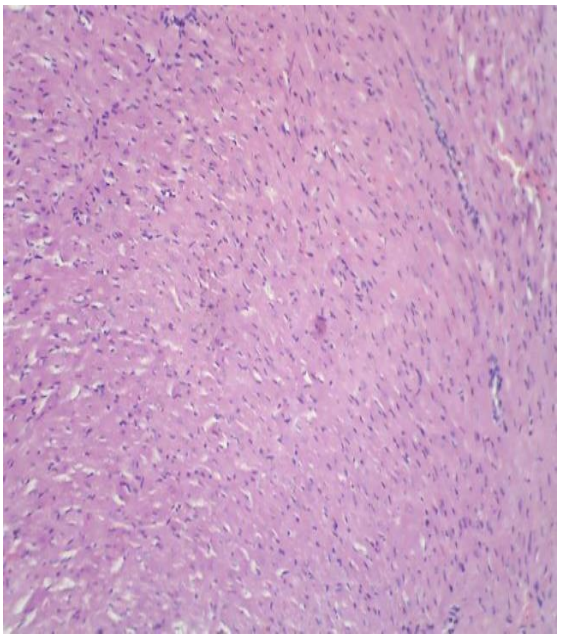


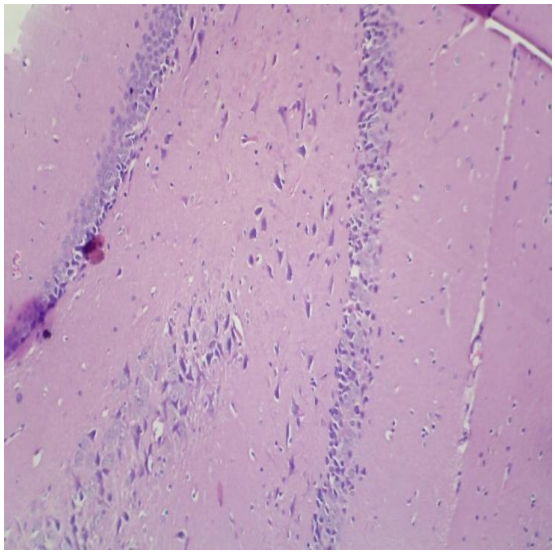
Higher dose

Microscopic appearance-

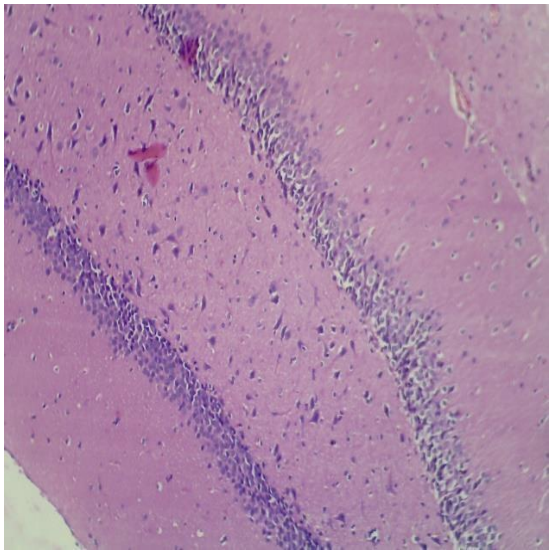
Section studies from the heart shows normal myocardium with myocytes. There is no evidence of myocytic degeneration or edema.

BRAIN

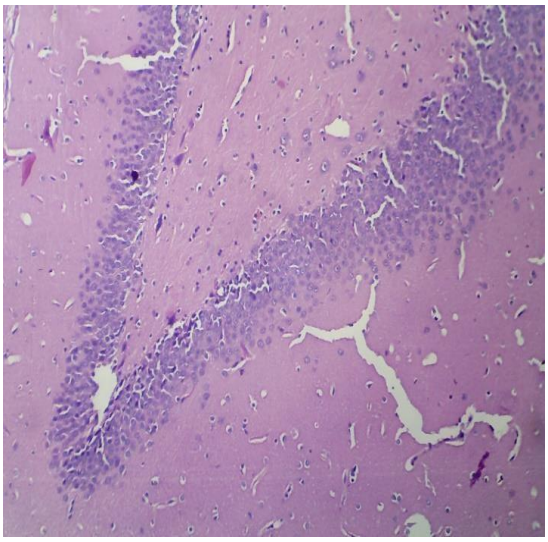
Figure 7- T.S of Rat Heart Showing Normal Cells In Sub Acute Toxicity Studies of Extract



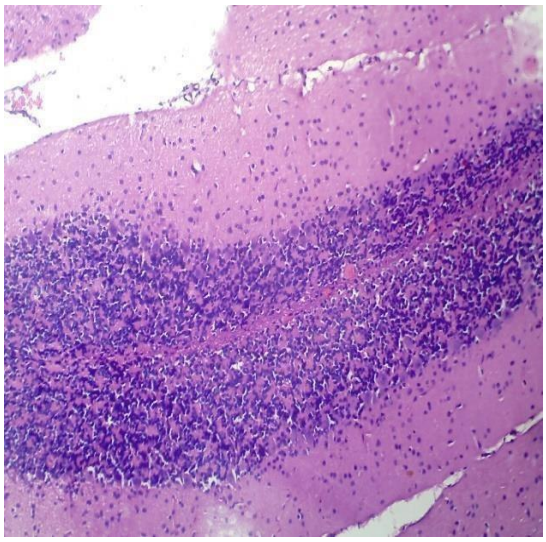
Control



Lower dose



Medium dose



Higher dose

Microscopic appearance-

Section studies from the brain shows normal cerebellum. Brain parenchyma, purkinjic cells and basal ganglion unremarkable. There is no evidence of inflammation and necrosis.

RESULT & DISSCUSION

In the sub-acute toxicity studies, no animal mortalities were observed in any of the study groups throughout the study period. The animals did not exhibit any treatment related abnormal behavioural traits. For all the dose level falling in the category NOAEL <100 mg/kg. The observations indicated that long-term administration of

the extract had no adverse effects on the general health of the animals. No significant differences were observed in body weights or food consumption of the animals of the treatment groups when compared with that of the control groups. Similarly, no significant changes in haematology parameters and blood biochemistry parameters of the animals of the treatment groups when compared with that of the control groups. However, on completion of the treatment animals were sacrificed, necropsied and pathological examination of vital organs such as liver, heart, kidney and brain were performed and result showed that cells were within normal.

REFERENCE

1. V. R. Kannan, G. S. Rajasekar, P. Rajesh, V. Balasubramanian, *et al.*, "Anti-diabetic activity on ethanolic extracts of fruits of terminalia chebula retz. Alloxan induced diabetic rats," *American Journal of Drug Discovery and Development*, 2012.
2. V. Jakus and N. Rietbrock, "Advanced glycation end-products and the progress of diabetic vascular complications," *Physiol. Res*, vol. 53, pp. 131-142, 2004.
3. P. K. Das, S. Bhattacharya, J. N. Pandey, and M. Biswas, "Antidiabetic activity of trapa natans fruit peel exctract against streptozotocin induced diabetic rats," *Global Journal of Pharmacology*, vol. 5, no. 3, pp. 186-190, 2011.
4. U. S. Sharma and A. Kumar, "Anti-diabetic effect of rubus ellipticus fruit extract in alloxan induced diabetic rats," *Journal of Diabetology*, vol. 2, no. 4, June 2011.
5. American Diabetes Association. Economic costs of diabetes in the US in 2002. Diabetes Care. 2003; 26: 917-932.
6. M. Velraj, M. Singh, V. Ravichandiran, S. Nirmala, and S. Ragala, "Antidiabetic activity of ethyl acetate and ethanolic extract of scindapsus officinalis fruit in alloxan induced diabetic rats," vol. 3, no. 3, pp. 1305-1310, July-Sept. 2011.
7. A. K. Datusalia, C. P. Dora, and S. Sharma, "Acute and chronic hypoglycemic activity of sida tiagii fruits in N5-streptozotocin diabetic rats," *Acta Poloniae Pharmaceutican Drug*

   Research, vol. 69, no. 4, pp. 699-706, 2012.
8. Marles RJ, Farnsworth N: Antidiabetic plants and their active constituents. Phytomedicine 1995, 2(2):137–189.
9. Harrison's Online > Part 16. Endocrinology and Metabolism > Section 1. Endocrinology> Chapter 344. Diabetes Mellitus> Epidemiology
10. Global burden of diabetes. International Diabetes federation. Diabetic atlas fifth edition 201, Brussels. Yach D, Hawkes C, Gould CL, Hofman KJ (2004) The global burden of chronic diseases: overcoming impediments to prevention and control. JAMA 291: 2616 2622.

11. Wild S, Roglic G, Green A, Sicree R, King H (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27: 1047-1053

12. American Diabetes Association (1998) Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 21: S5-S19.

13. Habtamu Wondifraw Baynest Classification, Pathophysiology, Diagnosis and Management of Diabetes Mellitus Baynes J Diabetes Metab 2015, 6:5

14. Kuttan R, Joy KL, Anti-diabetic activity of Picrorrhiza kurroa extract, J Ethnopharmacol 1999; 167: 143-8.

15. Crofton, K. M. (1992). Reflex modification and the Assessment of Sensory Dysfunction. In: Neurotoxicology (H. A. Tilson and C. L. Mitchell, Eds.), pp. 181-212, Raven Press, New York

16. MEYER, J. L., AND E. T. SCHULTZ. 1985. Migrating haemulid fishes as a source of nutrients and organic matter on coral reefs. Limnol. Oceanogr. 30: 146-156.

17. Karunanayake EH, Hearse D J, Mellows G. The metabolic fate and elimination of streptozocin. Biochemical Society Transactions 1975; 3: 410-14.7.