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Pharmacological effects of *Mallotus Philippensis* extracts of fruits in streptozotocin induced type-2 diabetes

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ABSTRACT

Aim

To evaluate the antidiabetic and antioxidant activity of *Mallotus philippensis* extracts of fruits in streptozotocin induced type 2 diabetes in rats and its complication in respect of cardiovascular complications.

Methods

The fruits of *Mallotus philippensis* were dried under shade and then powdered, and extracted with 1-1.5 liters of methanol by continuous hot percolation using Soxhlet apparatus at boiling point of methanol (62-65.5°C). Preliminary phytochemical studies were also carried out on extract. Diabetes was induced in overnight fasted male albino Wistar rats by a single i.p. injection of STZ at dose of 55 mg/kg. Group I served as untreated normal control while group II was considered as diabetic control. Group III, IV and V diabetic animals were treated with MEMP 150 mg/kg, MEMP 300 mg/kg and glibenclamide 500 mcg/kg b.w. respectively. During the study, body weight and fasting serum glucose level were taken at 0,7th and 15th day.At the end of study, animals in all groups were sacrificed, blood sample, pancreas and liver were collected. Biochemical parameter such as total cholesterol, HDL cholesterol, TG, LDL cholesterol, SGPT, SGOT, SALP, creatinine, and enzymatic antioxidants like SOD, GPx, catalase and lipid peroxidation from liver homogenate were determined. OGTT and histopathological studies of pancreas were performed.

Results

Oral administration of MEMP (150 mg/kg and 300 mg/kg b.w.) showed dose- related antidiabetic and antioxidant activities in diabetic animals , recovery of body weight, and demonstrated a significant reduction in fasting serum glucose, hypolipidaemic effect , protective effect on pancreas, reduction in serum transaminase and creatinine level.

Keywords: *Mallotus philippensis,* Streptozotocin, Antidiabetic, Antioxidant status,

INTRODUCTION

Treatment of type-I diabetes comprises insulin therapy & type-II with oral hypoglycemic in the initial phases & then a combination of insulin and oral hypoglycemic in the later phase.[1]

Classification of diabetes mellitus

Type 1 diabetes (β -cell destruction, usually leading to absolute insulin deficiency)

A. Immune mediated
B. Idiopathic

Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)

Other specific types

Causes of diabetes mellitus

Type 1 diabetes mellitus

1. Genetic predisposition.
2. Environnemental exposure: virus, toxin, stress.
3. Autoimmune reaction: β-cells that produce insulin in the pancreas are destroyed.

Type 2 diabetes mellitus

1. Insulin resistance: unable to utilize insulin that the body makes because of cell- receptor defect; glucose is unable to be absorbed into cells for fuel.
2. Decreased insulin secretion: pancreas does not secrete enough insulin in response to glucose levels.
3. Excess production of glucose from the liver is result of defective insulin secretory response; dawn phenomenon oms occur.

Gestational Diabetes Mellitus

1. Insulin resistance due to pregnancy
2. Genetic predisposition.

Characteristics of diabetes mellitus

Type 1 diabetes mellitus

1. Usually occurs before 30 years of age, but can occur at any age. Peak incidence occurs during puberty, around 10-12 years of age in girls and 12-14 years in boys.
2. Abrupt onset of signs and symptoms of hyperglycemia: increased thirst and hunger, frequent urination, weight loss, and fatigue.[2-4]

Ketosis prone

Type 2 diabetes mellitus

1. Usually occur after 30 years of age, but is now occurring in children and adolescent
2. Increased prevalence in some ethnic groups, e.g., African Americans, Hispanic/Latino, Native Americans, Asian Americans, and Pacific Islanders.
3. Strong genetic predisposition.
4. Frequently obese.
5. Not prone to ketoacidosis until late in course or with prolonged hyperglycemia.
6. May or may not have symptoms of hyperglycemia.
7. May also have extreme tiredness, blurred vision, delayed healing, numbness and tingling of hands and feet, recurring yeast infection.
8. Children between the ages of 10-19 that have one or more of the following are at an increased risk

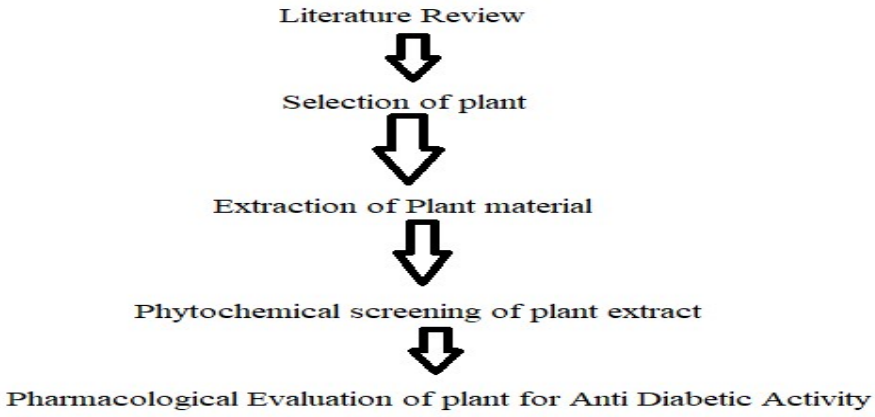
About Plant

Botanical name : *Mallotus philippensis*
Vernacular names : Kamala, Kampillaka, and Kapila, and locally known as Shendri.
Taxanomy:
Kingdom : Plantae
Order : Malpighiales
Family : Euphorbiaceae – spurge, euphorbes
Genus : Mallotus Lour.
Species : Mallotus philippensis (Lam.) Müll. Arg. – kamala tree

Uses

- Kampilu is very strong laxative (virechak) and it is very effective remedy to treat intestinal worms.
- External use of kampilu is used to relieve excessive irritation, scabies, eczema and it is good for easy healing of wounds and ulcers.
- Kamala powder, obtained from the skins of the fruits, is used as anthelmintic.
- The active compound is rottlerin.
- Rottlerin has been show to affect the fertility of female rats and guinea pigs, and is reportedly toxic to frogs, worms, and some fish species.[5]

Plan of Work



METHODS & METHODOLOGY

Collection, extraction and preliminary phyto- chemical studies

Collection and authentication of plant material

Fresh fruits of *Mallotus Philippensis* were collected from Survey of Medicinal Plants and Collection Unit, Department of AYUSH, Ministry of Health and Family Welfare, Government of India, Indira Nagar, Emerald, The Nilgiri District and authenticated by Dr.S.Rajan.

Preparation of plant extracts

The fruits of *Mallotus Philippensis* were dried under shade and then powdered with a mechanical grinder. The powder was passed through sieve No 40 and stored in an airtight container for further use.[6]

Extraction procedure

The coarse powder was extracted with 1-1.5 liters of methanol, continuously in soxhlet apparatus at boiling point of methanol (62-65.5°C), after completion of extraction, it was filtered and the solvent was removed by distillation under reduced pressure and washed with petroleum ether 2-3 times. The dried extract was stored in desiccator. % Yield (w/w) of the extract of *Mallotus Philippensis* in methanol is found to be 13.24 %.

Acute toxicity studies (LD50)

Preparation of dose

MEMP was dissolved in water, to prepare a dose of 3000mg/kg body weight of animal, and administered 1ml/100gm body weight of the animal.

Procedure

The procedure was divided into two phases, Phase I (observation made on day one), and Phase II (observed the animals since next 14 days). Two groups of healthy female rats (each group of 3 rats) were used for the experiment. First group animals were divided and fasted for 18 hours deprived from food, water withdrawn before 4 hours of the dosing, body weights were noted before and after dosing with MECB (3000mg/kg) orally. Individually animals were observed for 4 hours to see any clinical symptoms, any change in behavior or mortality. 6 hours post dosing again body weights recorded. Form the next day onwards, each day 1 hour the behavioral change, clinical symptoms or mortality was observed in the same animals for next 14 days and animal body weights were recorded on 8th and 14th day. The same procedure was repeated with another group of animals to nullify the errors.

Selection and preparation of dose for pharmacological screening

The MEMP was dissolved in water to prepare two dose levels, 150 and 300mg/kg body weight of the animals.

Methodology

Animal

Male Wistar rats (200-250 g) were procured from KGR college, India. They were housed in microlon boxes with standard laboratory diet and water *ad libitum*. The study was conducted after obtaining Institutional animal ethical committee clearance.[7-10]

Experimental design

Rats were divided into five groups, each group consisting of six animals. After overnight fasting (deprived of food for 16 hours had been allowed free access to water) diabetes was induced in group II ,III, IV,V by intraperitoneal injection of STZ dissolved in O.1M sodium citrate buffer at pH 4.5, at a dose of 55mg/kg body weight. The control rats received the same amount of 0.1 M sodium citrate buffer. The animals were allowed to drink 5% glucose solution overnight to overcome the drug- induced hypoglycemia[138]. Diabetes status was confirmed by estimating blood glucose levels after 72 hours of STZ injection. Animals showing fasting blood glucose levels above 250 mg/dl were selected for study.

Group I: Normal control received normal saline orally for 14 days.

Group II: Diabetic control received only STZ[138].

Group III: Received methanolic extract of *Mallotus Philippensis* orally at dose of 150 mg/kg b.w. for 14 days.

Group IV: Received methanolic extract of *Mallotus Philippensis* orally at dose of 300 mg/kg b.w. for 14 days .

Group V: Received glibenclamide orally at dose of 500 mcg/kg b.w. for 14 days[140].

Body weight of rats were taken on pre and post treatment i.e.

0, 7 th and 15 th day of post treatment by electronic balance .Fasting blood glucose level of rats were taken pre and post treatment i.e. 0, 7 th and 15 th day of post treatment.
At the end of experimental period, all the rats were sacrificed by cervical decapitation. Blood samples were collected, allowed to clot. Serum was separated by centrifuging at 2500 rpm for 15 min and analyzed for various biochemical parameters.

RESULTS

RESULT OF PRELIMINARY PHYTOCHEMICAL STUDIES

Results of preliminary phytochemical studies of methanolic extract of *Mallotus philippensis* fruits is presented in table 1.

Table 1: Result of preliminary phytochemical studies

Sl.No.	Test	Present(+) or absent(-)
1	Alkaloids	+
2	Carbohydrates	+
3	Glycosides	+
4	Fixed oils & fats	+
5	Gums & mucilage	+
6	Proteins & amino acids	+
7	Saponins	+
8	Tannins	+
9	PhytoSterols	-
10	Flavonoids	+

RESULTS OF 14 DAYS SINGLE DOSE ACUTE TOXICITY STUDY

Both in phase I and II observation in acute toxicity study carried out according to OECD guideline 423 (OECD, 1996), none of the rats showed observable signs of toxicity upon single administration of MEMP (3000mg/kg, p.o.) on day 1. Observations twice daily for 14 days also did not reveal any drug related observable changes. Similar experiment was repeated with another group of three animals to confirm the safety of the extract. (Table 2 to 7)

Table 2: Effect of methanolic extract of *Mallotus philippensis fruit* on body Weight in rats

Group	Body Weight(gm)			Change in body weight (%)
	0 day	7 th day	15 th day	
I Normal Control(Saline)	227.33±7.62	228.00±7.76	231.83±7.72^{ns}	+1.98
II Diabetic Control(STZ)	225.17±7.03	220.67±4.18	206.5±4.34*	-8.29
III(STZ+ MEMP 150 mg/kg)	230.83±8.60	223.00±8.40	236.5±9.06^{ns}	+2.46
IV(STZ+MEMP 300 mg/kg)	233.83±7.54	238.00±7.57	242.67±8.23^{ns}	+3.78
V (STZ+ Glibenclamide)	228.00±11.06	232.33±11.52	238.10±10.78^{ns}	+4.42

Table 3: Effect of methanolic extract of *Mallotus philippensis* fruit on serum glucose level in rats

Group	Serum glucose levels (mg/dl)			Change in Serum glucose (%)
	0 DAY	7 th DAY	15 th DAY	
I Normal Control(Saline)	101.36± 5.38	100.67± 5.83	97.49± 3.74	-3.82
II Diabetic Control(STZ)	315.10± 22.63^{a***}	316.30± 22.79^{a***}	314.46± 25.12^{a***}	-0.20
III(STZ+ MEMP 150 mg/kg)	287.69± 9.39^{b,ns}	256.17± 8.76^{b*}	211.20± 4.77^{b***}	-26.59
IV(STZ+ MEMP 300 mg/kg)	297.39± 16.10^{b,ns}	243.69± 10.16^{b**}	190.64± 3.67^{b***}	-35.90
V (STZ+ Glibenclamide)	290.79± 7.28^{b,ns}	210.38± 4.47^{b***}	132.71± 4.25^{b***}	-54.36

Table 4: *Mallotus philippensis*fruit on serum lipid profiles in rats

Group	Total Chole. (mg/dl)	HDLChole. (mg/dl)	TG (mg/dl)	LDL Chole. (mg/dl)
I Normal Control(Saline)	142.49± 5.04	48.56± 1.47	106.65± 4.85	72.59± 5.79
II Diabetic Control(STZ)	242.06± 9.12^{a***}	26.15± 1.15^{a***}	218.33± 4.58^{a***}	172.16± 8.98^{a***}
III(STZ+ MEMP 150 mg/kg)	210.73± 8.00^{b*}	38.91± 1.76^{b***}	196.65± 3.39^{b*}	132.49± 8.79^{b**}
IV(STZ+ MEMP 300 mg/kg)	197.08± 9.3^{b***}	40.37± 1.58^{b***}	188.72± 4.54^{b**}	120.44± 5.24^{b***}
V (STZ+ Glibenclamide)	193.96± 5.58^{b***}	48.84± 1.91^{b***}	133.56± 6.10^{b***}	88.40± 3.89^{b***}

Table 5: Effect of methanolic extract of *Mallotus philippensis* fruit on serum biomarkers in rats

Group	SGPT(U/L)	SGOT(U/L)	SALP(U/L)
I Normal Control(Saline)	54.31±3.35	60.83±3.88	138.24±3.66
II Diabetic Control(STZ)	136.18±4.33^{a***}	151.17±2.99^{a***}	248.46±4.05^{a***}
III(STZ+ MEMP 150 mg/kg)	117.02±4.72^{b**}	135.98±2.87^{b**}	233.79±2.69^{b,ns}
IV(STZ+ MEMP 300 mg/kg)	111.19±3.19^{b***}	122.10±0.97^{b***}	223.62±5.19^{b**}
V (STZ+ Glibenclamide)	74.91±2.22^{b***}	74.57±2.84^{b***}	167.30±5.25^{b***}

Table 6: Effect of methanolic extract of *Mallotus philippensis* fruit on serum glucose in rats in OGTT

Group	Serum glucose levels (mg/dl)				
	0 min	30 min	60 min	120 min	240 min
I (1ml dist. Water+2g/kg glucose)	69.4± 2.75	81.66± 1.13	80.72± 6.6	121.2± 12.00	129.53± 9.1
II (MEMP 150 mg/kg + 2g/kg glucose)	72± 5.30^{a,ns}	82.31± 1.1^{a,ns}	86.22± 5.5^{a,ns}	109.14± 2.12^{a,ns}	91.22± 3.10^{a**}
III (MEMP 300 mg/kg + 2g/kg glucose)	70.12± 3.22^{a,ns}	78.21± 1.65^{a,ns}	90.21± 4.74^{a,ns}	108.23± 1.20^{a,ns}	97.23± 4.25^{a**}

Table 7: Effect of methanolic extract of *Mallotus philippensis* fruit on liver SOD,Catalasse, GPx and Lipid Peroxidation

Group	SOD	LP	Cat.	GPx
I Normal Control(Saline)	11.53±0.36	13.67±0.89	7.51±0.31	7.01±0.18
II Diabetic Control(STZ)	3.98±0.4^{a***}	39.94±4.91^{a***}	3.09±0.23 ^{a***}	3.09±0.52^{a***}
III(STZ+ MEMP 150 mg/kg)	7.19±0.33^{b***}	30.12±2.51^{b,ns}	4.70±0.24^{b,ns}	4.04±0.08^{b,ns}
IV(STZ+ MEMP 300 mg/kg)	9.27±0.35^{b***}	23.86±0.78^{b*}	6.09±0.34^{b**}	4.78±0.40^{b*}
V (STZ+ Glibenclamide)	9.9±0.32^{b***}	19.28±1.85^{b**}	4.40±0.37 ^{b,ns}	4.78±0.40^{b*}

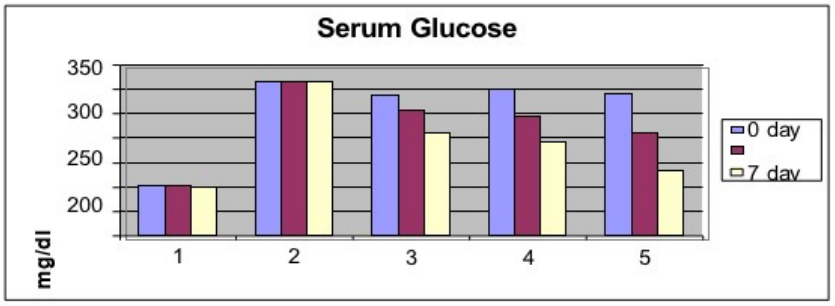


Fig 1: Effect of MEMP on serum glucose

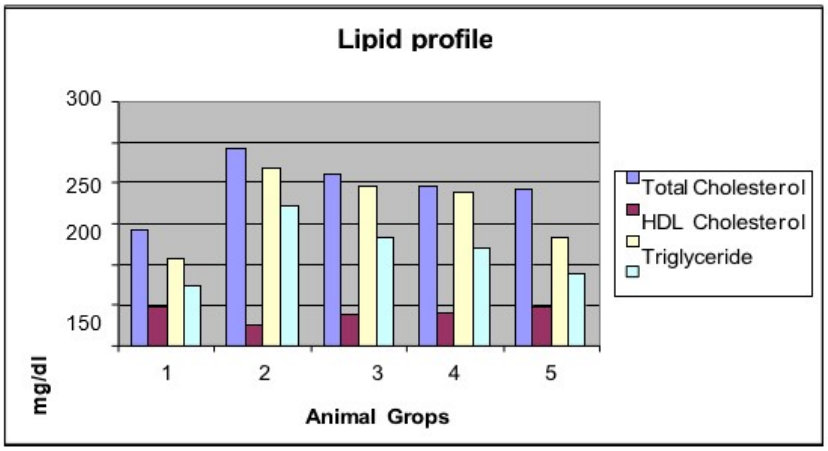


Fig 2: Effect of MEMP on lipid profile

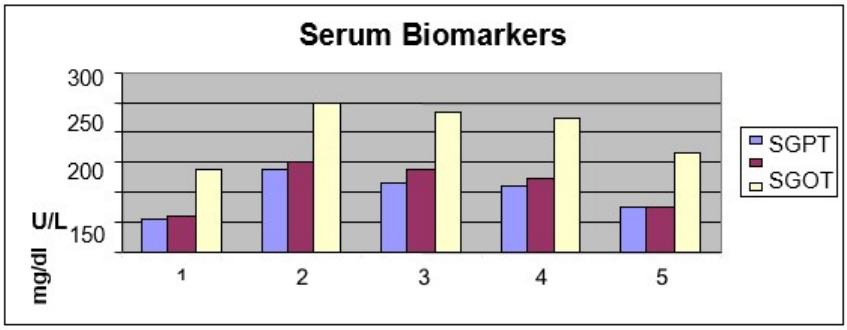
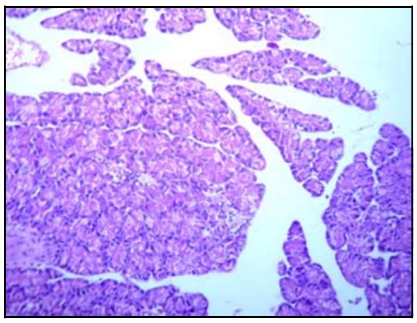
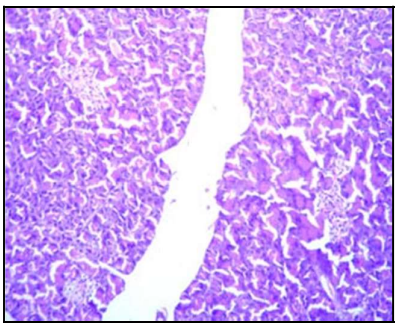


Fig 3 : Effect of MEMP on serum biomarkers

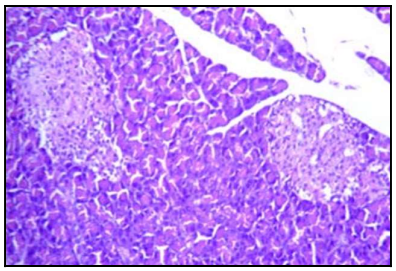
Pancreas lobules having light staining islets of pancreas



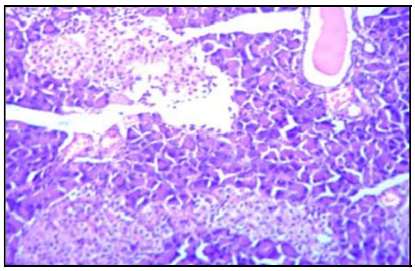
Normal control



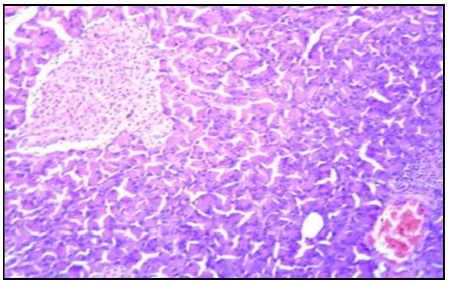
Diabetic control



MEMPB 150

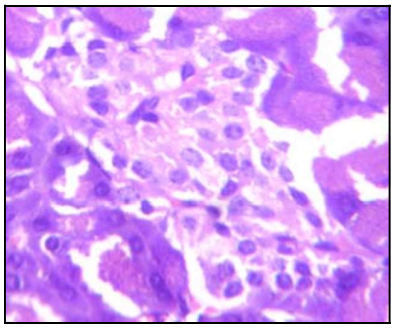


MEMP 300

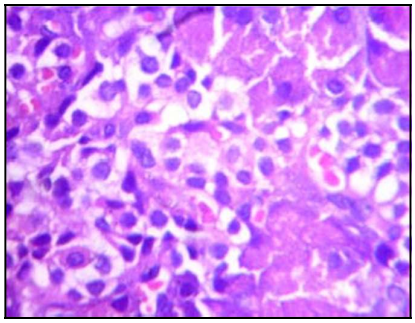


GLIBENCLAMIDE

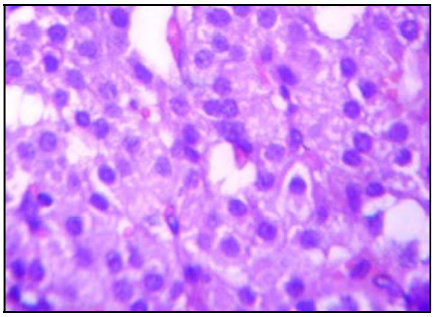
Islets of langerhans showing α and β cells



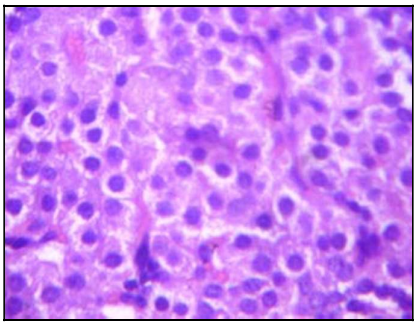
Normal control



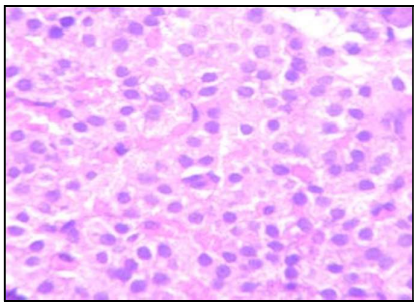
Diabetic control



MEMPB 150



MEMP 300



GLIBENCLAMIDE

Fig-9: Effect of MECB on kidney biochemical parameter

CONCLUSION

In conclusion, our data suggest methanolic extract of fruits of *Mallotus philippensis* possess potential antidiabetic activity as it lowers serum glucose level and significantly increases glucose tolerance. *Mallotus philippensis* also possess significant antihyperlipidemic activity as it lowers serum cholesterol and triglycerides levels, LDL cholesterol and increaese HDL cholesterol level. *Mallotus philippensis* did not exert any toxic effects in STZ-induced impaired kidney and liver functions. It was rather found to be improving kidney and liver functions. In addition, *Mallotus philippensis* possess potential antioxidant activity as it decrease lipid peroxidation and enhanced antioxidant status in diabetic rats. Our study indicates the role of oxidative stress in diabetes and antioxidant activities of *Mallotus philippensis* play a role in preventing diabetic complications and antidiabetic activity of *Mallotus philippensis* and 300 mg/kg of MECB was found to be more effective than 150 mg/kg MECB. It has also protective effect on pancreas that can be seen from histopathological studies. Thus, the pharmacological activities of methanolic extract of fruits of *Mallotus philippensis* may be due to the presence of vitamin C, vitamin E, Vitamin B complex, Carotenoids and Anthocyanins. Probable mechanism and active constituents of *Mallotus philippensis* responsible for antidiabetic and antioxidant activity reqiures further to be investigated.

Summary

Mallotus philippensis showed a dose-related antidiabetic and antioxidant activities in diabetic animals and demonstrated a significant reduction in fasting serum glucose, hypolipidaemic effect, protective effect on pancreas, reduction in serum transaminase activity which shows preventive action in hepatic damage, reduction in creatinine level which shows possible promising effect in renal dysfunctioning.

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