International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 1533-1553 www.ijprajournal.com ISSN: 2456-4494

Ameliorative Effect of Abutilon indicum Aqueous Extract in Chemical Induced Liver Cirrhosis in Experimental Rats

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Submitted: 10-12-2022 Accepted: 23-12-2022

ABSTRACTS
The leaves of Abutilon indicum (AI) were collected in and around the Banaras Hindu University campus personally in the month of July. The identification and authentication of the plant was done taxonomically. An herbarium of the leaves of Abutilon indicum were prepared and deposited in the Pharmacognosy division of Department of Pharmaceutics, IIT (BHU) Varanasi for further reference. Quality control studies for above plants part were conducted as per WHO, 1998 and IHP, 2002 guidelines. The quality control parameters studied were proximate analysis or quantitative physicochemical parameters. Less than 4% of alcoholic and water soluble extractive was obtained for AI. AI showed negligible levels of hemolytic activity. AI had very high swelling index because of presence of mucilaginous gland.
The preliminary phytochemical studies (Khandelwal KR, 2006) showed the presence of alkaloids, tannins, flavonoids in aqueous extracts of AI. The total phenolics (Hagerman A, et al., 2000) in the aqueous extract of AI equivalent to gallic acid was found to be 372.9948±0.02687mg / gram of dry weight extract respectively. The total tannin (Hagerman A, et al., 2000) in the aqueous extract of AI equivalent to tannic acid was found to be 29.9135016±0.125069 mg / gram of dry weight extract respectively. The total flavonoid content (Kumaran A, et al., 2006) of AI was found to be 0.065273±0.00287 mg / gm plant extract in rutin equivalent respectively. The total flavanol content (Kumaran A, et al., 2006) of AI was found to be 3.14±0.025 mg/gm plant extract in rutin equivalent respectively. The alkaloid content (Swain T et al., 1959) of AI was found to be 6.367889±0.0246117. The total antioxidant capacity of AI was found 21.03801±0.01334. The percentage inhibition (IC_{50}) obtained by DPPH free radical scavenging activity method for AI were 87.98±3.406528. The IC_{50} obtained by scavenging of superoxide radical by alkaline DMSO method were 39.38±3.403591 for AI respectively. The percentage inhibition obtained by scavenging of hydrogen peroxide method for AI were 30.478667±2.008269. The percentage inhibition obtained by assay of nitric oxide were 73.95±2.447427 for AI.
Acute toxicity studies of aqueous extract of AI were conducted by following OECD, 423 guidelines. There was no mortality or any signs of behavioral changes or toxicity observed after oral administration of AI up to the dose level of 4000mg/kg body weight in experimental rats. The liver cirrhosis protective activity study for AI was performed by using ethanol, paracetamol & carbon tetrachloride induced rat models. The parameters studied were estimation of different liver enzymes i.e. AST, ALT, SALP & bilirubin. Also, in vivo antioxidant parameters were studied and Histopathological studies performed. The results showed dose dependent liver cirrhosis protective activity, AI-300 being the most effective, by decreasing the level of liver enzymes, total carbohydrate to protein ratio, causing cell proliferation, increasing CAT and decreasing LPO and SOD activity. The study establishes quality control parameters and liver cirrhosis protective activity of aqueous extract of Abutilon indicum.
Keywords: Abutilon indicum, In Vivo Antioxidant, In Vitro Antioxidant**,** Liver Cirrhosis, Ameliorative Effect

I. INTRODUCTION:

Herbal Medicine

Herbal medicines also called as traditional medicine or phytomedicines are plant based medicines used to prevent and treat a disease, or to recover good health(Kumar, Bajaj et al. 2006). As per World Health Organization (WHO), Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products that contain as active ingredients parts of plants, or other plant materials, or combinations(Dubey, Kumar et al. 2004).

Plants have been defined by plant derived material or preparation with therapeutic or other human benefits which contain either raw or processed ingredients with one or other plants.

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Volume 7, Issue 6 Nov-Dec 2022, pp: 1533-1553 www.ijprajournal.com ISSN: 2456-4494

Medical scientists are very much serious towards emerging trends of disease due to drug resistance posing a challenge to global health care regarding their treatment(Sofowora 1982). It has been realized that indigenous systems of medicine based on plant drugs may provide a better option to mankind thus plant material and herbal remedies derived from are occupying a substantial proportion of global drug market. Thus, the demandforplant-based medicine is accelerating(Tilburt and Kaptchuk 2008).

In recent years Synergy research in Phytomedicine has also established itself as a new key activity. One of the main aim of this research to find a scientific rational for the therapeutic superiority of many herbal drug extracts derived from traditional medicine as compared with single constituents there of (Wagner, 2011). Synergy effects of the mixture of bioactive constituents and their byproducts contained in plant extracts are claimed to be responsible for the improved effectiveness of many extracts.

Its multi-target effects, in which the single constituents of a mono- or multi-extract combination affect not only one single target, but several targets such as enzymes, substrates, metabolites, receptors, ion channels, transport proteins, DNA/RNA, ribosomes or monoclonal or antibodies(Wagner and Ulrich-Merzenich 2009). Also, Due to its multi target effect they may help in thereduced effectiveness / side effects of conventional medicines.

Today, plant and plant extracts are back into prominence because the efficacy of conventional medicines such as antibiotics, which once had near-universal effectiveness against serious infections, is on wane. InAyurveda (traditional Indian medicine) about 2,000 plant species are considered to have medicinal value, while the Chinese pharmacopeia lists over 5,700 traditional medicines, most of which are of plant origin. Ayurveda based drug discovery uses “reverse pharmacology”, in which drug are first identified based on large-scale use in the population, then validated in clinical trials.

Active chemical constituents present in extract so its better to isolate or make an enriched fraction of that constituents. This is important or helpful for proper dosing.

Quality control standardization of herbal drugs

Standardization of herbal medicine is the process of prescribing a set of standards or inherent characteristics, constant parameters, definitive qualitative and quantitative values that carry an assurance of quality, efficacy, safety and reproducibility of the drug (Kunle et al, 2012). Due to the commercialization of herbal medicine in recent year assurance of safety, quality and efficacy of medicinal plants herbal product have become an important issue. The herbal raw material is prone to a lot of variation due to several factors such as the identity of the plant and seasonal variation (depending on the time of collection), the ecotypic, genotypic and phenotypic variations, drying and storage conditions and the presence of xenobiotic (Dixit et al., 2008).

Standardization of herbal medicine on the basis of pharmacognostic aspects includes physicochemical evaluation and determination of microbial and heavy metal contamination.

(1) Preliminary testing for the presence of the different phytochemical classes.

(2) Quantification of Phytochemical groups of interests (e.g. total alkaloids, total phenolics, total triterpenoid acids, total tannins etc.),

Pharmacological standardization of herbal drugs has been applied to achieve a better therapeutic efficacy and biological effect. The assays on living animals on their intact or isolated organs can indicate the effect of the drug or their preparations. These assays are known as Biological assays or pharmacological evaluations. It is, however safe to assume that based on human experience in various cultures the use of toxic plant ingredients has already been largely eliminated and recent reports of toxicity could largely be due to misidentification and over-dosing of certain constituents (Mosihuzzaman and Iqbal,2008).

Introduction of Liver cirrhosis

Liver damage ranges from acute hepatitis, cirrhosis, fatty liver and chronic hepatitis to hepatocellular carcinoma. The mechanisms indicated for liver damage include apoptosis, necrosis, inflammation, immune responses, fibrosis, and ischemia(Tilburt and Kaptchuk 2008). The liver produces large amounts of oxygen free radicals in the course of detoxifying xenobiotics and toxic substances, and oxidative stress caused by oxygen free radicals has been shown to be linked to liver diseases, such as hepatotoxicity and other liver pathological conditions(Tocher, Fonseca-Madrigal et al. 2002).

Treatment options for common liver diseases are often very problematic. The effectiveness of treatments such as interferon, colchicine, penicillamine and corticosteroids are inconsistent at best, and the incidence of side-effects is profound and very often the treatments are worse than the disease. Physicians and patients are in need of

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effective therapeutic agents with a low incidence of side effects. Several plants extract potentially constitutes such a group. In recent years, researchers have examined the effects of plants used traditionally by indigenous healers and herbalists to support liver function and treat diseases of the liver. In most cases, research has borne out the traditional experience and wisdom by discovering the mechanisms and modes of action of these plants, as well as confirming the therapeutic effectiveness of certain plants or plant extracts in clinical studies.

II. MATERIALS AND METHODS:

Plant material and extraction preparation:

The plant shrub of Abutilon indicum was collected in and around the Banaras Hindu University Ayurveda garden in Department of Botany personally in the month of July. The identification and authentication of root were done by Prof. N. K. Dubey Professor, Department of Botany, Institute of Science, Banaras Hindu University, Varanasi.

Modified Cold Maceration Method:

Dried leaf of Abutilon indicum were thoroughly washed and shade dried for one week at room temperature. The dried roots were coarsely ground into homogenous powder using a mechanical grinder, passed through a 60-mesh sieve and stored at room temperature until extraction. The homogenous leaf powdered drug 10 kg firstly activated in Microwave by following Microwave assisted extraction for 30 second for 3 cycle. This is followed by 96 hours of cold maceration with intermittent stirring. The extracts were filtered and concentrated under reduced pressure and kept in desiccators until use. The extracts were filtered and concentrated under reduced pressure and kept in desiccators until use.

Methods:

Quality control studies of plant material has been performed based upon the physiochemical parameters. This ensures and helps us to cross validate the quality raw material to be used for biological evaluation.

Determination of quantitative physicochemical parameters:

The list of various physiochemical parameters is beneficial for the standardization and quality control of heterogeneous plant secondary metabolites. The methods for all physicochemical parameters were done as per the method of WHO 1998. The parameters done were: Determination of Foreign matter, Determination of Loss on drying, Determination of Ash Value, Total Ash - Acid Insoluble Ash & Water soluble Ash, Extractive value, Determination of Swelling Index, Determination of Foaming Index, Hemolytic index and Heavy metals estimation.

Quantitative phytochemical estimation

It included estimation of total phenolic, total tannin, total flavonoid and total flavanol content. The aqueous extracts of AI were used for this.

Determination of total phenolic content

The estimation of total phenolic content was carried out by folincoicalteau calorimetric method as by Hagerman A, et al., 2000 with some modifications.

Estimation of total tannin content

The estimation of total tannin content was also done as per the method proposed by Hagerman et al., 2000 with some modifications.

Estimation of total flavonoid

The determination of the total flavonoid content was carried out based on the aluminum chloride method using rutin as the standard reference compound (Kumaran et al, 2006).

Estimation of total flavanol content

The method was done as per the procedure proposed by Kumaran et al, 2006.

In vitro antioxidant studies:

The study dealt with total antioxidant capacity, DPPH radical scavenging activity, alkaline dimethyl sulfoxide (DMSO) method for scavenging of the superoxide radical and the hydrogen peroxide scavenging activity.

Antioxidant activity assay:

The antioxidant activity of the ethanolic extracts of AI was evaluated by the phospho- molybdenum method according to the procedure of Prieto et al, 1999.

DPPH Free Radical Scavenging Activity Assay:

The free radical scavenging activity of the extracts, based on the scavenging activity of the stable 1, 1-diphenyl-2-picrylhydrazyl (DPPH) free radical, was determined by the method described by Braca et al, 2001.

Scavenging of superoxide radical by alkaline DMSO method:

The scavenging of super oxide radical by alkaline DMSO was done based on the method proposed by Elizabethan et al, 1990.

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Scavenging of hydrogen peroxide:
The scavenging of hydrogen peroxide radical was carried away based on the method proposed by Jay Prakash et al, 2004.
Assay of reducing power:
Assay of reducing power was carried out by potassium ferricyanide method (Yildirim, 2001).

Experimental Animals:

Adult Charles Foster strain of albino rats (150 ± 20g) of either sex, were obtained from Central Animal House, Institute of Medical Sciences, B.H.U. and were randomly distributed into different experimental groups. The rats were housed in groups of six in polypropylene cages at an ambient temperature of 25-degree Celsius ± 1 deg celsius and 45-55% RH, with a 12:12 hr. light/dark cycle. Animals were provided with commercial food pellets and water ad libitum. Animals were acclimatized for at least one week before using them for experiments and exposed only once to every experiment. "Principles of laboratory animal care" (NIH publication number 85-23, revised 1985) guidelines were followed.

Acute Toxicity Study:

Acute toxicity studies of water-soluble extract of Abutilon indicum were conducted by following OECD, 423 guidelines. Animals were fasted prior to dosing. Following the period of fasting, the animals were weighed and the fraction was administered. The fraction was administered in a single dose. After the fraction was administered, the food was withheld for further 3-4 hours. Different doses (100, 200, 300 mg/kg body weight, p.o.) of fractions of AI were administered to different group of rats separately and observed after dosing at least once during the first 30 minutes, periodically during the first 24 hours, with special attention given during the first 4 hours and daily thereafter, for a total of 6 days.

AMELIORATIVE LIVER CIRRHOSIS STUDY
Drugs and Chemicals
The following drugs and chemicals were used in the present study. All the reagents and chemicals used were of analytical grade.

- Abutilon indicum aqueous leaf extract was prepared from extraction method.
- Silymarin used as a standard hepatoprotective agent in all the experiments was obtained from Micro Labs Ltd., Bangalore. Paracetamol used to induce hepatotoxicity was obtained from Sun Pharm, Baroda.
- Carbon Tetrachloride used to induce hepatotoxicity was obtained from mMerck Ltd., Mumbai.
- Ethanol used to induce hepatotoxicity was obtained from mMerck Ltd., Mumbai.
- The biochemical kits for estimation of SGOT, SGPT, ALP and Bilirubin

were obtained from SPAN Diagnostics LTD., Surat.

DRUG TREATMENT:
Paracetamol-induced hepatotoxicity:

Paracetamol (Acetaminophen) was suspended in 0.3% sodium CMC and administered orally at a dose of 250mg/kg. This dose is known to cause liver damage in rats (Mitra et al., 1998). Rats were divided into 6 groups (6 per group). Group 1, the normal control group was given a single daily dose of 0.3% sodium CMC p.o., for 4 days. Group 2, the paracetamol control group received a daily dose of 0.3% sodium CMC for 4 days and paracetamol suspension (250mg/kg, p.o.) on day 3. Animals of group 3-4 were given a single dose of paracetamol (250mg/kg, p.o.) & group 3 animals received Silymarin at a dose of 100mg/kg, p.o., on all the 4 days and paracetamol suspension (250mg/kg, p.o.), 30 min after Silymarin administration only on the day 3. Groups 4, 5 and 6 received a daily dose of AI extract p.o., for all 4 days (100, 200, 300mg/kg, respectively) and paracetamol suspension (250mg/kg p.o.) only on day 3, 30 min after AI extract administration. The animals were sacrificed 48hrs after paracetamol administration by mild ether anesthesia. From all the six groups, blood and liver samples were collected for biochemical and histological studies (Shyamal et al., 2006).

Carbon tetrachloride induced hepatotoxicity:

CCl_4 is diluted using paraffin in a 1:1 ratio. This diluted CCl_4 (toxin) is used for inducing hepatotoxicity in rats. Rats were divided into 6 groups, each containing 6 rats. Group 1(normal control group) was treated with a single daily dose of 0.3% CMC (1ml, p.o.) on all 5 days and liquid paraffin (1ml/kg, i.p.) on day 3. Animals of group 2 (CCl_4 control group were treated with Silymarin, 100mg/kg, p.o.) for 5 days; and on day 3, a single dose of CCl_4 (2ml/kg, i.p.) was administered 30 min after Silymarin administration. Animals of groups 4-6 were treated with AL extract p.o. (100, 200 and 300mg/kg respectively) for 5 days; then a single dose of ccl4 (2ml/kg, i.p.) was administered

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on day 3, 30 min after AI extract administration (Shyamal et al., 2006; suja et al., 2004). Blood and liver samples were collected from all the 6 groups for biochemical and histochemical studies.

Ethanol-induced hepatotoxicity:

Ethanolic diluted using TDW in a 1:1 ratio. This diluted ethanol (toxin) is used for inducing hepatotoxicity in rats. Rats were divided into 6 groups, each containing 6 rats. Group 1(normal control group) was treated with a single daily dose of 0.3% CMC (1ml, p.o.) on all 5 days and TDW (1ml/kg, i.p.) on day 3. Animals of group 2 (ethanol control group) were treated with Silymarin, 100mg/kg, p.o.) for 5 days; and on day 3, a single dose of ethanol (2ml/kg, i.p.) was administered 30 min after Silymarin administration. Animals of groups 4-6 were treated with AL extract p.o. (100, 200 and 300mg/kg respectively) for 5 days; then a single dose of ethanol (2ml/kg, i.p.) was administered on day 3, 30 min after AI extract administration (Shyamal et al., 2006; suja et al., 2004). Blood and liver samples were collected from all the 6 groups for biochemical and histochemical studies.

Determination of serum alanine transaminase (ALT):
ALT catalyzes the following reaction:
α-ketoglutarate + L-Alanine-Pyruvate + L-Glutamate
Pyruvate reacts with 2, 4 dinitrophenyl hydrazine (DNPH) to give pyruvate hydrazone, which gives brown color in alkaline condition and reading was measured by an instrument biochemistry analyzer.
Reagents (supplied in kit):
1: buffered Alanine α-ketoglutarate substrate, 2: DNPH color reagent, 3: Sodium Hydroxide, 4N, 4: Working pyruvate standard, 2Mm

Preparation of working solutions:
Solution1: 1 ml of reagent 3 is diluted to 10 ml with distilled water.
Procedure:
0.25ml of buffered Alanine α-ketoglutarate substrate was incubated at 37 c for 5 minutes. To this substrate, 0.005 ml of DNPH color reagent (reagent2) was added, mixed well and allowed to stand at room temperature for 20 minutes followed by the addition of 2.5 ml of solution 1. The mixture was allowed to stand at room temperature for 10 min. and then reading was taken by using biochemistry analyzer CHEM5-Plus V2 (Erba manheir®).

Determination of serum Aspartate Transaminase (AST):
Principle:
AST catalyzes the following reaction:
α- ketoglutarate+L-Aspartate→oxaloacetate+ L-Glutamate
Oxaloacetate so formed reacts with 2, 4 dinitrophenyl hydrazine (DNPH) to give oxaloacetate hydrazone, which gives brown color in alkaline condition and then reading was measured by an instrument biochemistry analyzer.
Reagents (supplied in kit):
1: buffered aspartate α- ketoglutarate substrate, 2: DNPH color reagent, 3: sodium hydroxide, 4 4: working pyruvate standard, 2Mm

Preparation of working solutions:
Solution 1:1ml of reagent 3 is diluted to 10 ml with distilled water.
Procedure:
0.25 ml of buffered aspartate α- ketoglutarate substrate was incubated at 37 c for 5 minutes. To this substrate, 0.005 ml of serum was added, mixed well and again incubated at 37 c for 60 minutes. Further to this 0.25 ml of DNPH color reagent (reagent2) was added, mixed well and allowed to stand at room temp for 20 minutes and then reading taken by using biochemistry analyzer CHEM5-Plus V2(Erba manheir®).
Determination of Serum Alkaline Phosphate (SALP):

Principle:
Alkaline phosphatase from serum converts Phenyl phosphate to inorganic phosphate and phenol at PH 10. Phenol so formed reacts in alkaline medium with 4-aminoantipyrine in presence of oxidizing agent potassium ferricyanide and forms an orange-red complex. This colored complex is estimated by an instrument biochemistry analyzer (Kind and King, 1954).
Phenyl phosphate→ Phenol + Phosphate
Phenol+ 4-aminoantipyrine→orange red complex

Reagents (supplied in the kit):
1: buffered substrate, PH 10, 2: chromogen reagent, 3: phenol standard, 10mg%
Preparation of working solution:
The vial containing reagent1 (buffered substrate) is reconstituted with 2.2 ml of distilled water.

Procedure:
To each test tubes designated as blank(B), Standard(S), Test(T) and Control(C), 0.5 ml of working buffered substrate and 1.5 ml of distilled

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water is added, mixed well and incubated at 37 c for 3 minutes. Then 0.05 ml of reagent 3 is added to test tube S and 0.05 ml of serum to test tube C and then reading taken by using biochemistry analyzer CHEM5-Plus V2(Erba manheir®).

Determination of Serum Bilirubin:
Principle:
Direct or conjugated bilirubin couples with diazotised sulfanilic acid, forming azobilirubin, a red purple colored product in acidic medium, whereas unconjugated bilirubin is diazotized only in presence of methanol. The intensity of the red-purple color so developed above is measured by an instrument biochemistry analyzer (Malloy and Evelyn, 1937).
Reagents (supplied in the kit):
1: Diazo A, 2: Diazo B, 3: Diazo blank, 4: Methanol, 5: Artificial standard (10 mg% bilirubin)
Preparation of working solution:
Just before use, 1 ml of reagent 1 is mixed with 0.03 ml of reagent 2.
Procedure:
To each test tubes designated as direct (D1), Direct blank(D2), Total(T1) and total blank(T2), 0.1 ml of serum and 0.9 ml of distilled water is added. 0.25 ml of reagent 3 is added to T2 and D2. 0.25 ml of the working solution is added to T1 and D1. 1.25 ml of distilled water is added to D1 and D2. 1.25ml of methanol is added to T1 and T2.
The test tubes T1 and T2 are kept in dark for 30 minutes and reading was measured by an instrument biochemistry analyzer.

IN VIVO ANTIOXIDANT STUDIES
Preparation of tissue homogenate

At the end of study i.e on 6th day animals were sacrificed by cervical dislocation. The liver was immediately excised out, washed in ice-cold saline to remove the blood. The liver was sliced into pieces and 10% tissue homogenate was prepared with 0.125 M Tris-HCL buffer (PH 7.5). after centrifugation at 10,000× g for 10 min, the clear supernatant obtained was used for various biochemical estimation.

Estimation of lipid peroxidation

Lipid peroxidation in liver was estimated colorimetrically by measuring thiobarbituric acid reactive substances (TBARS) using the methods of Nehius and samuelson (1968). In brief,0.1 ml of tissue homogenate was treated with2 ml of TBA-trichloroacetic acid -HCL reagent (0.37% TBA, 0.25 M HCL, and 15% TCA, 1:1:1 ratio), placed for 15 min in a water bath and then cooled and centrifuge at 3500×g for 10 min room temperature, the absorbance of clear supernatant was measured at 535 nm against a reference blank.value were expressed as mM/100 g-tissue.

Estimation of catalase activity

Catalase (CAT) was estimated by the method of Sinha (1972). The reaction mixture (1.5 ml) contained 1.0 ml of 0.01M phosphate buffer (PH 7.0), 0.1 ml of tissue homogenate and 0.4 ml of H_2O_2. The reaction was stopped by the addition of 2.0 ml of dichromate-acetic acid reagent (5% potassium dichromate and glacial acetic acid were mixed in 1:3 ratio). Then the absorbance was read at 620 nm; CAT activity was expressed as µM of H2O2 consumed/min/mg protein.

Estimation of superoxide dismutase (SOD) activity

The activity of SOD was assayed by the method of Kakkar et al. (1984). 0.5 ml of tissue homogenate was diluted with 1 ml of water. In the mixture, 2.5 ml of ethanol and 1.5 ml of chloroform (all reagents chilled) were added and shaken for 1 min at 4^{o}c then centrifuge. The assay mixture contained 1.2 ml of sodium pyrophosphate buffer (0.025 M, PH 8.3), 0.1 ml of 186 µM PMS, 0.3 ml of 30 µM NBT,0.2 ml of 780 µM NADH, appropriately diluted enzyme preparation and water in a total volume of 3 ml. The reaction was started by the addition of NADH. After incubation at 30^{0} c for 90 sec,the reaction was stopped by the addition of 1 ml glacial acetic acid. The reaction mixture was stirred vigorously and shaken with 4 ml of n-butanol. The intensity of the chromogen in the butanol layer was measured at 560 nm against butanol blank. A system devoid of enzyme served as control. One unit of the enzyme activity is defined as the enzyme reaction. Which gave 50% inhibition of NBT reduction in one minute under the assay conditions.

Histopathological Examination

We performed the histopathological examination of any organ or cell for knowing the actual condition of that organ or cell.

Liver pieces were preserved in 10% formaldehyde solution for histopathological study. The pieces of liver were and dehydrated with a sequence of ethanol solution and embedded in paraffin wax. Sections of about 4-6 µm thickness were cut. They were stained with hematoxylin, eosin and photographed using a photomicroscope.

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III. RESULT:

"Table 1.1. Physiochemical Evaluation of the Crude DrugAbutilon indicum"

Sl. No.	Standardization Parameters	%W/W(Mean±SEM)
1.	Total ash	4.42±0.12
2.	Acid insoluble ash	2.44±1.21
3.	Water soluble ash	2.41±0.09
4.	Sulphated ash	3.42±0.02
5.	Alcohol soluble extractive value	20.44±1.09
6.	Water soluble extractive value	12.72±2.89
7.	Loss on drying 1	6.94±0.54

1.1 Quantitative Phytochemical Estimation

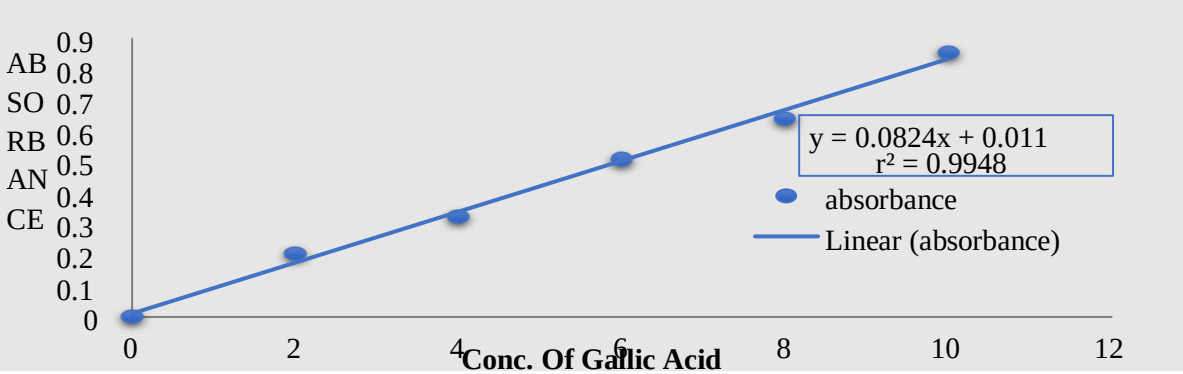
1.1.1Total phenolic content:

Standard calibration curve Fig. was plotted by taking absorbance of different concentrations of Gallic acid. The total phenolic in the aqueous equivalent to Gallic acid found to be as follow:

"Table 1.2. Standard calibration curve data for gallic acid"

Concentration (µg/ml)	Absorbance (765nm)
0	0
2	0.2053
4	0.325167
6	0.5106
8	0.641133 `
10	0.854567

"Fig. 1.1.Standard calibration curve for total phenolic content (Gallic acid as standard)"



"Table 1.3. Total phenolic content (At 765 nm) of AI"

Aqueous extract	Absorbance	Total phenolic content (mg/gm dry weight extract
AI	0.7514	372.9948±0.02687

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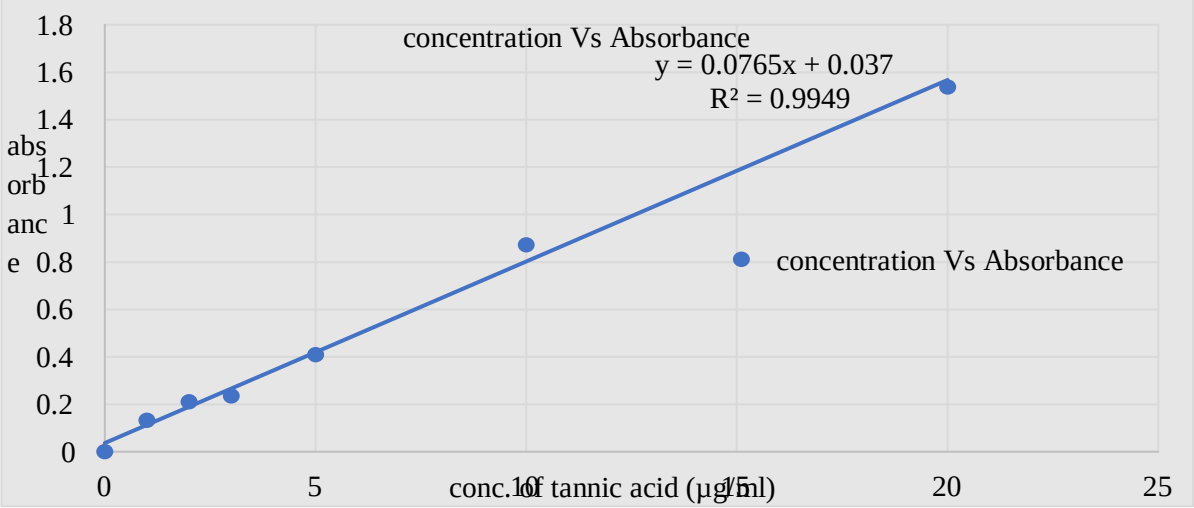
1.1.2 Total Tannin content:

Standard calibration curve Fig. was plotted by taking absorbance of different concentrations of tannic acid. Tab shows absorbance for AI. The total tannin in the aqueous extract equivalent to tannic acid was found:

"Table 1.4.Standard calibration curve data for Tannic acid"

Concentration (µg/ml)	Absorbance (775nm)
0	0
1	0132867
2	0.210433
3	0.235067
5	0.409333
10	0.872133
20	1.537232



"Table 1.5. Total Tannin content (at 775 nm) of AI"

Aqueous extract	Absorbance	Total phenolic content (mg/gm dry weight extract
AI	0.2648	29.9135016±0.125069

1.1.3Total flavonoid content

"Table 1.6.Absorbance table for standard Rutin"

Sr.no.	Standard compound	Absorbance (Blank)(415nm)		Absorbance (standard) (415nm)
1	Rutin	0.020		0.405

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"Table 1.7.Absorbance table for total flavonoid content of AI"

Sr.no.	Aqueous extract	Absorbance (Blank)(415nm)	Absorbance (standard) (415nm)
1	AI	0.050	0.175

Calculation:
The amount of flavonoids in plant extracts in Rutin equivalents (RE) was calculated by the following formula:
$X= (A. m_o) / (A_o. m)$

Where X is the flavonoid content, mg/g plant extract in RE, A is the absorption of plant extract solution, Ao is the absorption of standard Rutin solution, m is the weight of plant extract, mg and $m_{o.}$ is the weight of Rutin in the solution, mg.

"Table 1.8.Total Flavonoid content of AI"

Aqueous extract	Flavonoid content (mg/ml)	Total Flavonoid content (mg/gm plant extract)
AI	0.062555	0.065273±0.00287

1.1.4 Total flavanol content

"Table 1.9.Absorbance table for standard rutin"

Sr.no.	Standard compound	Absorbance (Blank)(440nm)	Absorbance (standard) (415nm)
1	Rutin	1.065±0.001	3.310±0.000

"Table 1.1.0Absorbance table for total flavanol content of AI"

Sr.no.	Aqueous extract	Absorbance (Blank)(440nm)	Absorbance (standard) (440nm)
1	AI	1.089±0.000	02.0122±0.011

Calculation:
The amount of flavanol's in plant extracts in Rutin equivalents (RE) was calculated by the following formula:
$X= (A. m_o) / (A_o. m)$

Where X is the flavanol content, mg/g plant extract in RE, A is the absorption of plant extract solution, Ao is the absorption of standard Rutin solution, m is the weight of plant extract, mg and m_o is the weight of Rutin in the solution, mg.

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"Table 1.11. Total Flavanol content of AI"

Aqueous extract	Flavonoid content (mg/ml)	Total Flavonoid content(mg/gm plant extract)
AI	0.036±0.0941	3.14±0.025mg

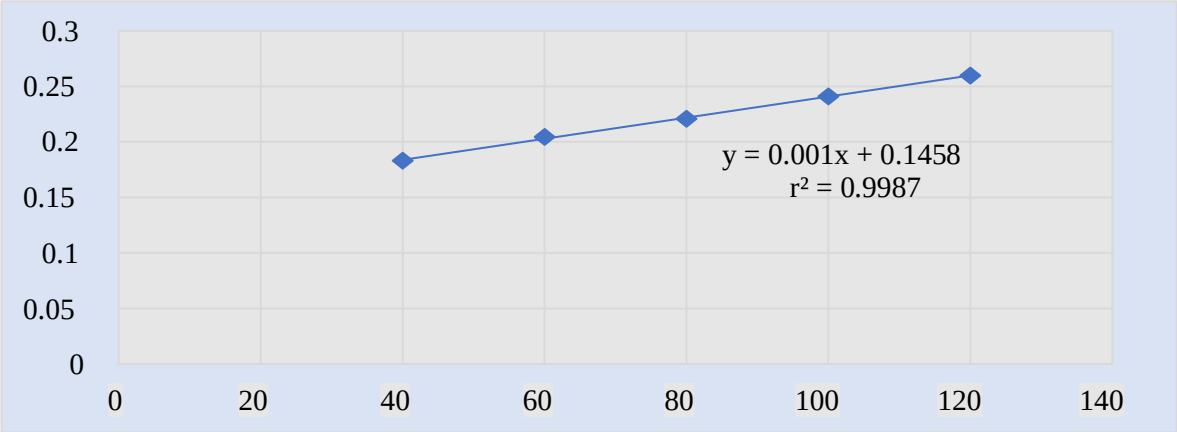
1.2.5 Total Alkaloid content

Standard calibration curve Fig. was plotted by taking absorbance of different concentrations of atropine. The total alkaloid in the aqueous equivalent to atropine found to be as follow:

"Table 1.12.Standard calibration curve data for Gallic acid"

Concentration (µg/ml)	Absorbance (765nm)
40	0.18296
60	0.204467
80	0.220773
100	0.2409
120	0.259767

"Fig 1.3.Standard calibration curve for total alkaloid content (Atropine as standard)"



"Table 1.13.Total alkaloid content of AI"

Aqueous extract	Absorbance	Total alkaloid content (mg/gm dry weight extract
AI	0.1514	6.367889±0.024611

1.2 IN VITRO ANTIOXIDANT STUDIES

1.2.1. Total Antioxidant capacity

From the standard graph plotted the results for the samples were interpolated

"Table 1.14."

Concentration(µg/ml)	Absorbance(695nm)
0	0
25	0.305033

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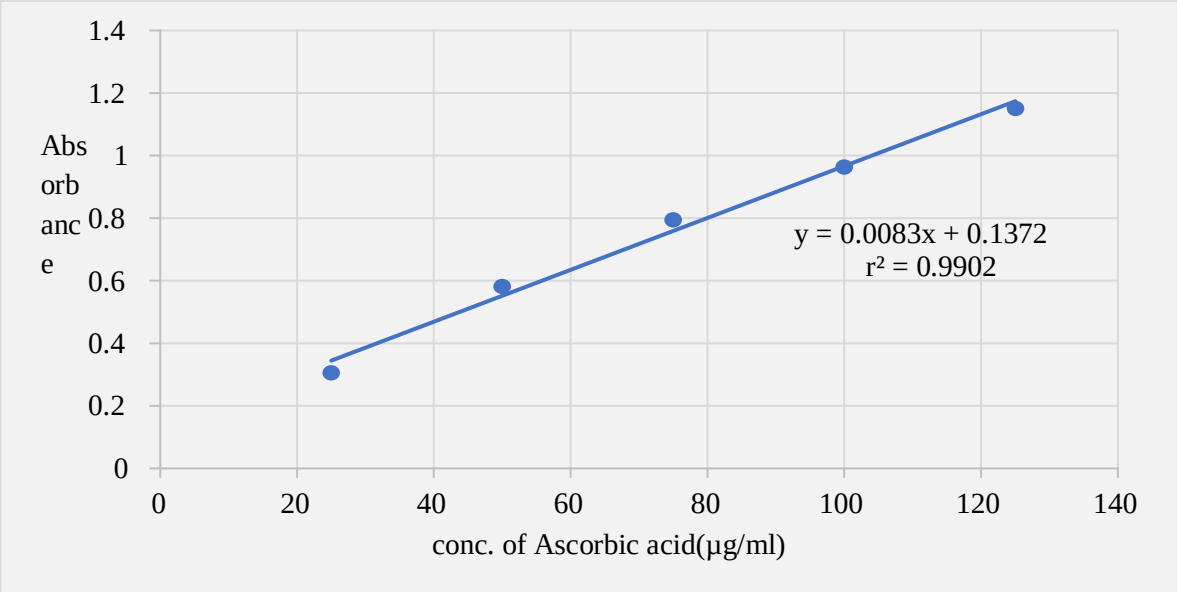
50	0.581467
75	0.79487
100	0.9637
125	1.1505

"Fig. 1.4.Standard calibration curve for Ascorbic acid"



"Table 1.15.Absorbance table for AI for total antioxidant capacity"

Absorbance (695nm) (Mean±SEM.*)
0.311867±0.000524

"Table 1.16. Result for total Antioxidant capacity"

Total antioxidant capacity(Mean±SEM.*)
21.03801±0.01334

1.2.2 DPPH free radical scavenging activity
From the standard graph plotted the results for the samples were interpolated:
Result for Percentage inhibition (IC_{50}) - AA & AI (DPPH)

"Table 1.17."

Percentage Inhibition (IC_{50}), Mean± S.E.M*. (µg/ml)		
Sample	Ascorbic acid	AI
IC_{50}(µg/ml)	46.58333±1.590991	87.98±3.406528

3.2.3. Scavenging of superoxide radical by Alkaline DMSO method
From the standard graph plotted the results for the samples were interpolated:
Result for Percentage inhibition (IC_{50}) (Alkaline DMSO)

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"Table 1.18."

Percentage Inhibition (IC_{50}), Mean± S.E.M*. (µg/ml)		
Sample	Ascorbic acid	AI
IC_{50}(µg/ml)	21.94333±2.410065	39.38±3.403591

1.2.4 Scavenging of Hydrogen peroxide
From the standard graph plotted the results for the samples were interpolated:
Result for Percentage inhibition (IC_{50}) AA & AI (Hydrogen peroxide)

"Table 1.19."

* Percentage Inhibition (IC_{50}), Mean± S.E.M*. (µg/ml)		
Sample	Ascorbic acid	AI
IC_{50}(µg/ml)	15.825±0.857017	44.58667±2.008269

1.2.5 Assay of Nitric oxide
From the standard graph plotted the results for the samples were interpolated:
Result for Percentage inhibition(IC_{50}) AA& AI (Nitric oxide)

"Table 1.20."

* Percentage Inhibition (IC_{50}), Mean± S.E.M*. (µg/ml)		
Sample	Ascorbic acid	AI
IC_{50}(µg/ml)	31.92333±1.502519	73.95±2.447427

1.3 LIVER ENZYMES ASSAY
"Table 1.21.Effect of AI Leaf extract treatment on serum enzymes in Paracetamol treated animals"

GROUP	AST(IU/L)	ALT(IU/L)	SALP (KA UNITS/100 ml)	BILIRUBIN (mg%)
Normal control	85.88±3.05	33.44±1.30	70.01±1.80	0.45±0.024
Paracetamol control(250mg/kg)	210.10±1.3	182.21±1.4	142.91±1.52	2.50±0.030
Paracetamol(250mg/kg) + Silymarin(100mg/kg)	94.05±1.30 ***	40.05±2.10 ***	72.91±1.85 ***	0.65±0.020 ***
Paracetamol(250mg/kg) + extract(100mg/kg)	163.01±4.2 *** †††	90.01±1.55 *** †††	122.5±2.30 *** †††	1.06±0.041 *** †††
Paracetamol(250mg/kg) + extract(200mg/kg)	124.16±2.4 *** †††	70.6±1.38 *** †††	95.30±3.25 *** †††	0.85±0.030 *** †††

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Paracetamol(250mg/kg) + extract(300mg/kg)	103.8±1.30 ***	47.00±3.01 ***	77.40±2.71 ***	0.69±0.05 ***

Values are mean ± S.E.M., n=6 animals in each group.
* Compared to the ccl4 group, † Compared to Silymarin group.
***, ††† represents statistical significance: p<0.001.

"Table 1.22. Effect of AI Leaf extract treatment on serum enzymes in Carbon tetrachloride (CCL_4) treated animals"

GROUP	AST (IU/L)	ALT (IU/L)	SALP (KA UNITS/100 m)	BILIRUBIN (mg%)
Normal control	88.88±5.05	35.44±1.30	74.01±1.80	0.51±0.014
CCl_4 control(2ml/kg)	200.10±1.3	177.21±1.40	146.91±1.52	1.09±0.060
CCl_4 (2ml/kg) +Silymarin (100mg/kg)	99.05±1.30 ***	48.05±2.10 ***	78.91±1.85 ***	0.45±0.050 ***
CCl_4(2ml/kg) + extract(100mg/kg)	173.01±4.2 *** †††	96.01±1.55 *** †††	132.5±2.30 *** †††	0.99±0.01 *** †††
CCL_4(2ml/kg) + extract(200mg/kg)	129.16±2.40 *** †††	72.6±1.38 *** †††	95.60±3.25 *** †††	0.88±0.090 *** †††
CCL_4(2ml/kg) + extract(300mg/kg)	106.8±1.30 ***	45.70±3.01 ***	87.49±2.71 ***	0.74±0.08 ***

Values are mean ± S.E.M., n=6 animals in each group.
* Compared to the ccl4 group, † Compared to Silymarin group.
***, ††† represents statistical significance<0.01 and p<0.001 respectively.

"Table 1.23. Effect of AI Leaf extract treatment on serum enzymes in Ethanol treated animals"

GROUP	AST (IU/L)	ALT (IU/L)	SALP (KA UNITS/100 ml)	BILIRUBIN (mg%)
Normal control	85.88±3.05	37.44±1.30	70.91±1.80	0.49±0.024
control (2 ml/kg)	209.05±1.30	184.21±1.40	143.91±1.52	1.98±0.030
Ethanol (2 ml/kg) +Silymarin (100mg/kg)	94.05±1.30 ***	42.05±2.10 ***	73.51±1.85 ***	0.59±0.020 ***
Ethanol (2 ml/kg) + extract(100mg/kg)	163.01±4.2 0 *** †††	92.01±1.55 *** †††	122.3±2.30 *** †††	1.65±0.091 *** †††
Ethanol (2 ml/kg) + extract(200mg/kg)	124.16±2.40 *** †††	72.6±1.38 *** †††	96.50±3.25 *** †††	0.79±0.00 *** †††

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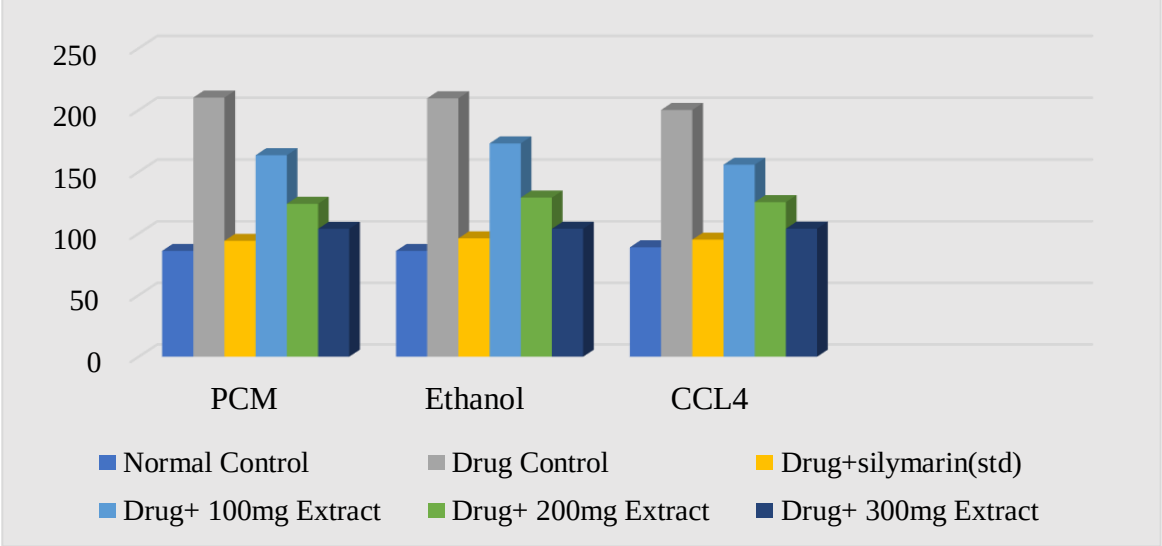
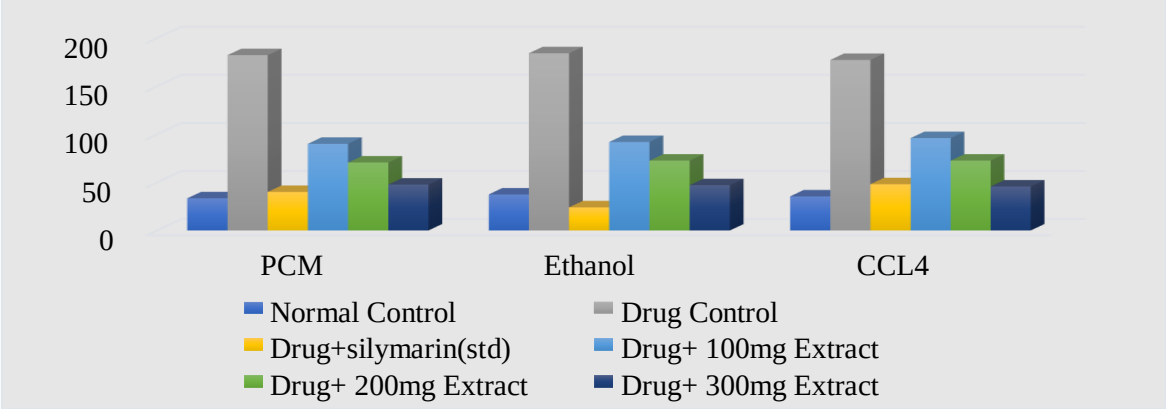
Ethanol (2 ml/kg) + extract(300mg/kg)	103.8±1.30 ***	47.70±3.01 ***	78.95±2.71 ***	0.65±0.05 ***

Values are mean ± S.E.M., n=6 animals in each group.
* Compared to the ccl4 group, † Compared to Silymarin group.
***, ††† represents statistical significance: p<0.001

"Fig. 1.5. Graphical comparisonof serum Aspartate Transaminase(AST) in all 3 different models"



"Fig. 1.6. Graphical Comparison of serum alanine transaminase (ALT) in all 3 different models"



"Fig. 1.7. Graphical Comparison of Serum Alkaline Phosphate (SALP) in all 3 different"

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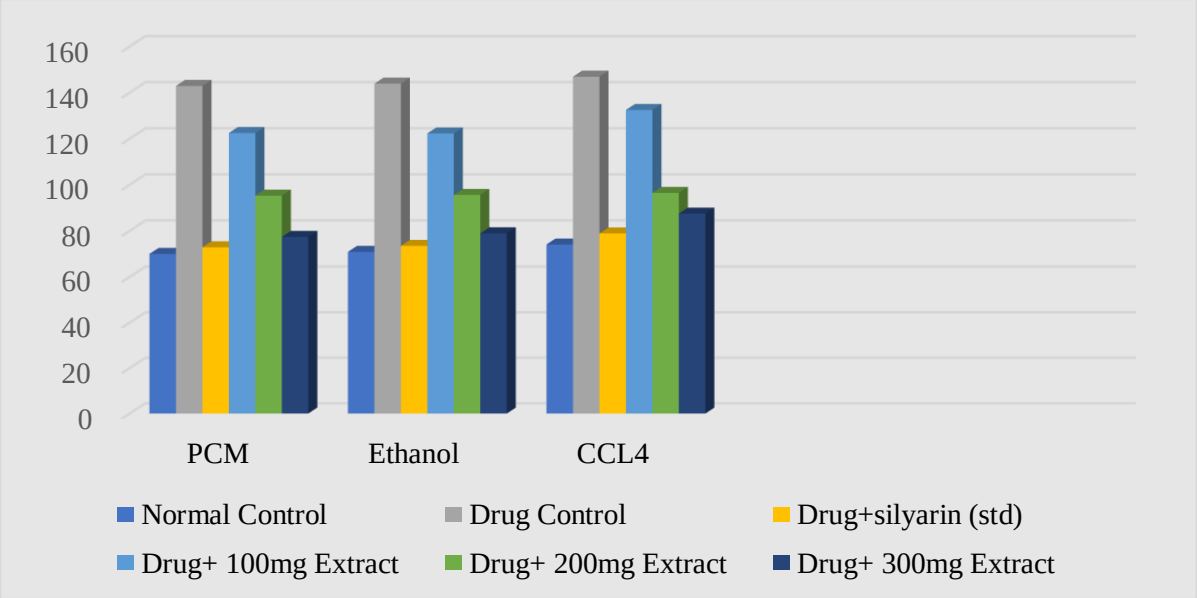
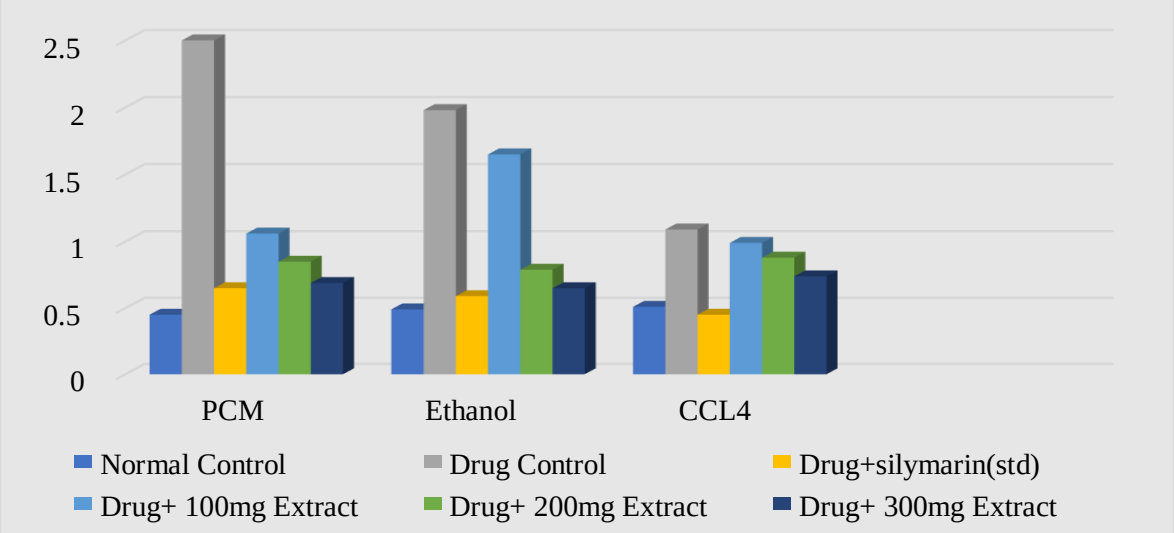


"Fig. 1.8. Graphical Comparison of Serum Bilirubin in all 3 different models"



1.4 IN VIVO ANTIOXIDANT STUDIES

"Table 1.24. Effect of AI extract on lipid peroxidation, catalase and SOD levels in CCL_4 treated animals"

GROUP	MDA (nmol/mg protein)	CATALASE (nmol/min/mg protein)	SOD (units/mg protein)
Normal control	0.48±0.016	5.24±0.050	1.63±0.078
CCL4 Control(2ml/kg)	1.62±0.039	2.84±0.039	0.86±0.023
CCL4(2ml/kg) + Silymarin(100mg/kg)	0.51±0.022 ***	5.46±0.026 ***	1.40±0.042 ***

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CCL4 (2ml/kg) + extract(100mg/kg)	0.99±0.033 *** †††	3.42±0.035 *** †††	1.14±0.058 *** ††
CCL4 (2ml/kg) + extract(200mg/kg)	0.76±0.047 *** †††	4.23± 0.073 *** †††	1.23±0.076 *** ††
CCL4 (2ml/kg) + extract(300mg/kg)	0.58±0.022 ***	5.33±0.064	1.43±0.026 ***

Values are mean± S.E.M., n=6 animals in each group.
*Compared to CCL4 group, † Compared to Silymarin group
*, †, **, †† and ***, ††† represents statistical significance at p<0.05, p<0.01, p<0.001 respectively.

"Table 1.25. Effect of AI extract on lipid peroxidation, catalase and SOD levels in Paracetamol treated animal"

GROUP	MDA (nmol/mg protein)	CATALASE (mmol/min/mg protein)	SOD (units/mg protein)
Normal control	0.46±0.023	5.16±0.081	1.66±0.023
Paracetamol Control(2ml/kg)	1.49±0.045	2.70±0.054	0.89±0.039
Paracetamol (2ml/kg) + Silymarin(100mg/kg)	0.50±0.020 ***	5.21±0.084 ***	1.36±0.063 ***
Paracetamol(2ml/kg) + extract(100mg/kg)	0.95±0.039 *** †††	3.66±0.043 *** †††	1.10±0.011 *** ††
Paracetamol (2ml/kg) + extract(200mg/kg)	0.73±0.020 *** †††	4.81± 0.051 *** †††	1.24±0.020 *** ††
Paracetamol(2ml/kg) + extract(300mg/kg)	0.55±0.034 ***	5.19±0.013	1.41±0.077 ***

Values are mean± S.E.M., n=6 animals in each group.
*Compared to CCL4 group, † Compared to Silymarin group
*, †, **, †† and ***, ††† represents statistical significance at p<0.05, p<0.01, p<0.001 respectively.

"Table 1.26. Effect of AI extract on lipid peroxidation, catalase and SOD levels in Ethanol treated animals"

GROUP	MDA (nmol/mg protein)	CATALASE (mmol/min/mg protein)	SOD (units/mg protein)
Normal control	0.45±0.093	5.16±0.020	1.65±0.083
Paracetamol Control(2ml/kg)	1.50±0.005	2.90±0.014	0.90±0.019
Paracetamol (2ml/kg) + Silymarin(100mg/kg)	0.49±0.020 ***	5.11±0.084 ***	1.35±0.063 ***
Paracetamol (2ml/ kg) + extract(100mg/kg)	0.95±0.039 *** †††	3.66±0.043 *** †††	1.09±0.081 *** ††
Paracetamol (2ml/kg) + extract(200mg/kg)	0.73±0.020 *** †††	4.81± 0.051 *** †††	1.24±0.020 *** ††
Paracetamol(2ml/kg) + extract(300mg/kg)	0.55±0.034 ***	5.19±0.013	1.41±0.077 ***

Values are mean± S.E.M., n=6 animals in each group.
*Compared to CCL4 group, † Compared to Silymarin group
*, †, **, †† and ***, ††† represents statistical significance at p<0.05, p<0.01, p<0.001 respect

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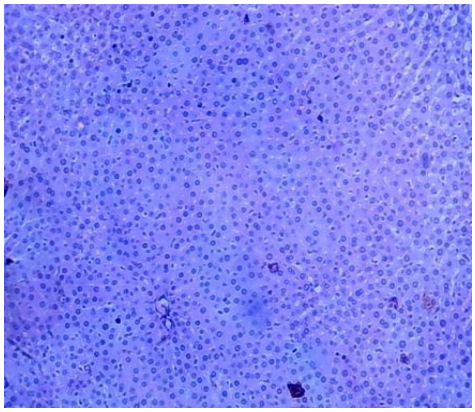
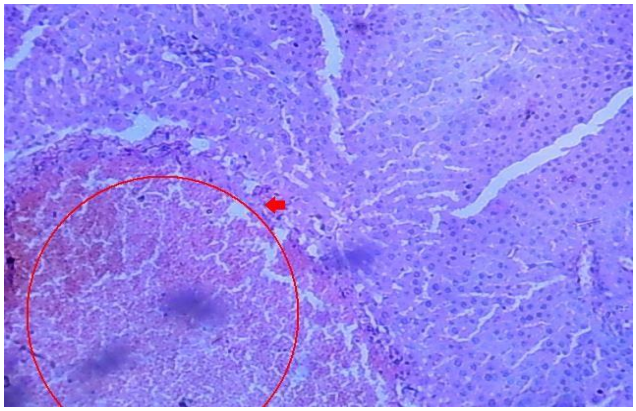
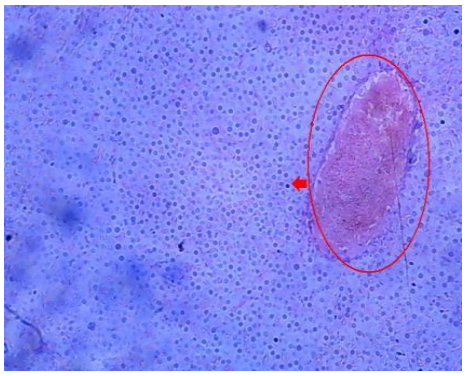
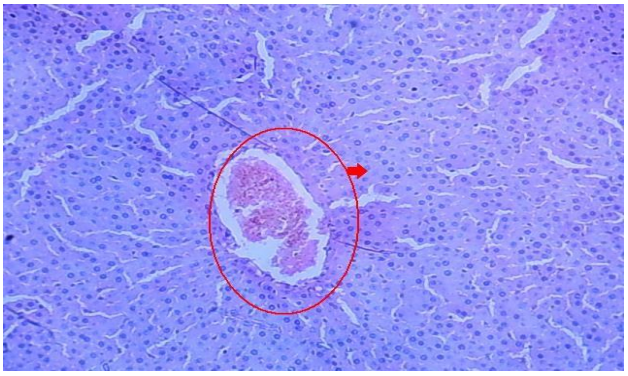
1.5 Histopathological Studies



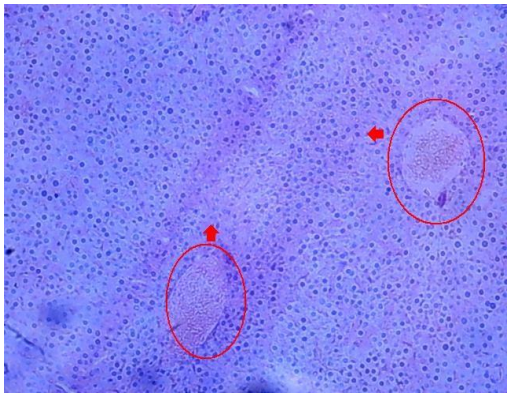


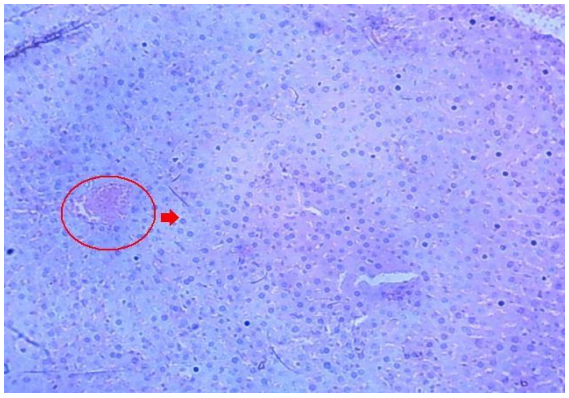
"Fig.1.9. Liver section of normal "Fig.1.10 Liver section of PCM control group"treated group"





"Fig.1.11. Liver section of Extract (100mg/kg) + PCM treated" "Fig.1.12. Liver section of Extract (200mg/kg) + PCM treated rats"





"Fig.1.13. Liver section of Extract
"Fig.1.1.4 Liver section of PCM + Silymarin(100mg/kg)"
(300mg/kg) +PCM treated rats"

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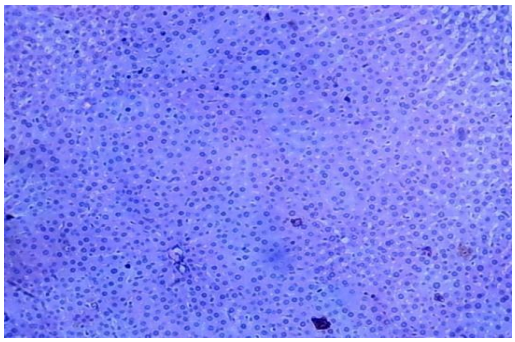
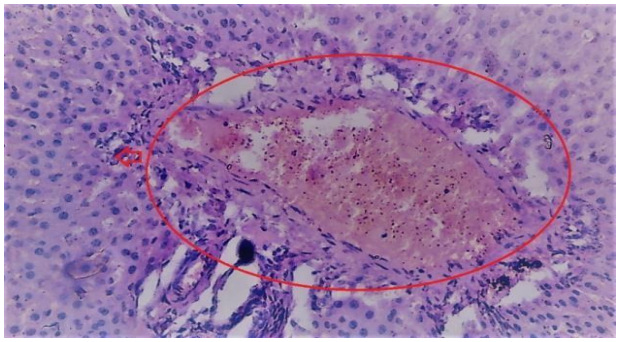
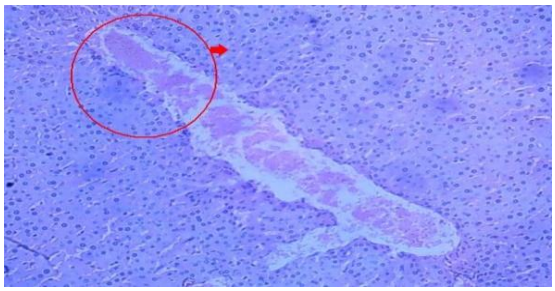
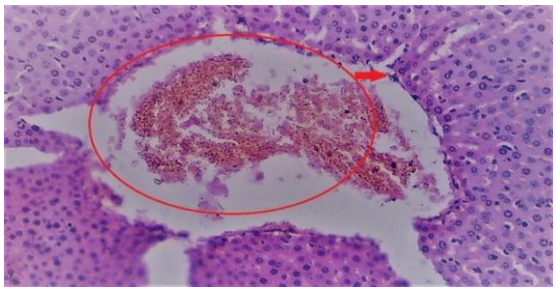




" Fig.1.15. Liver section of normal group" Fig.1.16. Liver section of Ethanol control group"

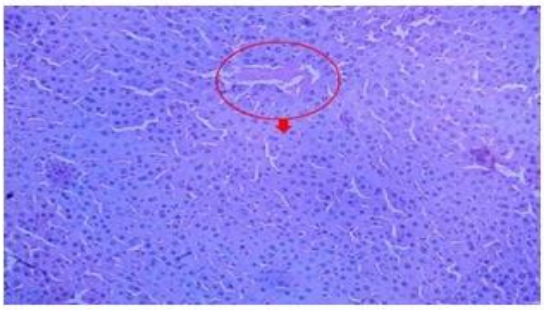
Control"

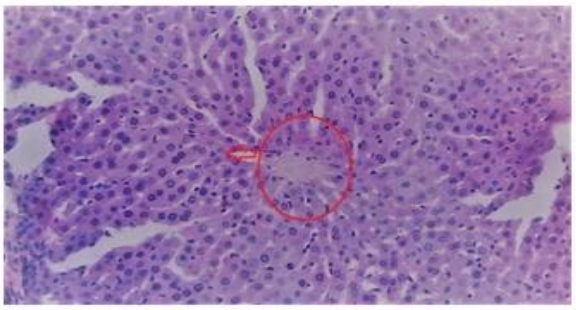




"Fig.1.17. Liver section of Extract (100mg/kg) + Ethanol treated rats"

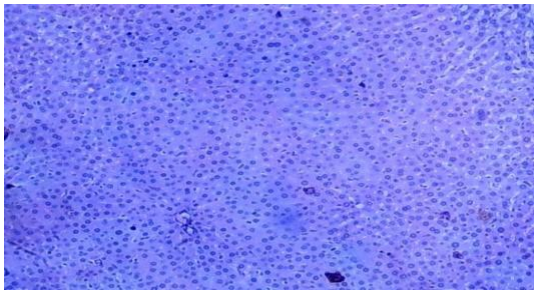
"Fig.1.18. Liver section of Extract (200mg/kg) + Ethanol treated rats"

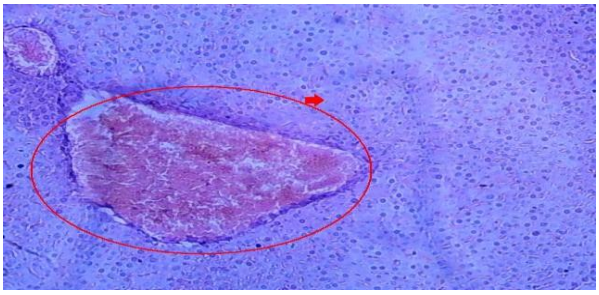




"Fig.1.19. Liver section of Extract (300mg/ kg) treated"

"Fig.1.20. Liver section of Silymarin (100mg/kg) + Ethanol treated rats + Ethanol rats"





"Fig.1.21. Liver section of normal control group"

"Fig.1.22. Liver section of CCL_4 control treated group"

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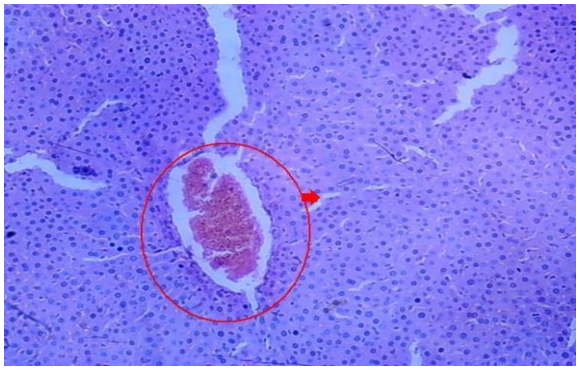
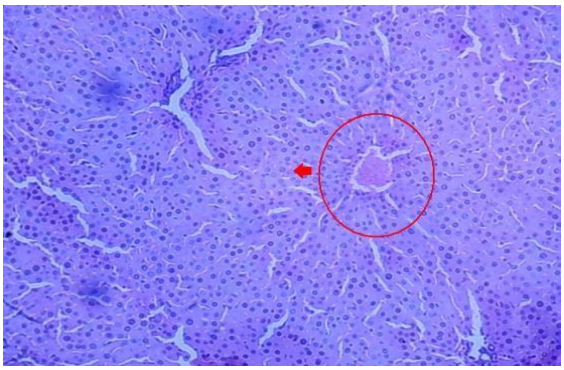
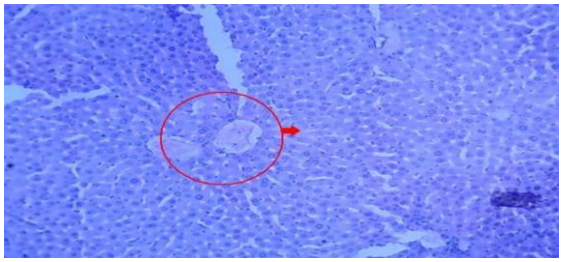


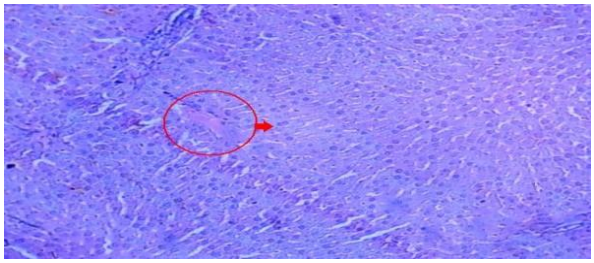
"Fig.1.23. Liver section of Extract (100mg/kg) + CCL_4 treated rats"



"Fig.1.24. Liver section of (200mg/kg) Extract+ CCL_4 treated rats"



"Fig.1.24. Liver section of Extract (300 mg/kg) + CCl_4 treated rats"



" Fig.1.25. Liver section of Silymarin (100mg/kg) + CCL_4 treated rats"

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