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HEPATO PROTECTIVE AND ANTIOXIDANT EFFECT OF CNIDOSCOLUS PHYLLACANTHUS AGAINST D-GALACTOSAMINE INDUCED OXIDATIVE STRESS IN RATS

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ABSTRACT

The aim of present investigation is one of traditionally used herbs anti-Hepatotoxicity being assessed against the Paracetamol induced Hepatotoxicity in rats.The drug related Hepatotoxicity is uncommon for many drugs, the reported incidence is between 1 in 10,000- its true incidence is difficult to determine. The number may be much higher,because of underreporting,difficulties in detection or diagnosis,and incomplete observation of persons exposed (Navarro and John, 2006). Paracetamol treatment caused significant ($p<0.001$) decreases in the activities of SOD, catalase, GPx and GSH level in liver tissue when compared to control group.. Silymarin-treated animals also showed a significant ($p<0.001$) increase in antioxidant enzymes, namely SOD, catalase, GPx activities and GSH level compared to paracetamol-treated rats.To understand the effect of the extract on liver, histology of liver was performed. Firstly, Organoleptic Characterization of plant extract was performed. Organoleptic evaluations are subjective, sensory judgements. They can involve eyeing, feeling and taste of the extract to the judge its appearance, coour, integrity, texture and flavours. The organoleptic characters of alcoholic extract of Cnidoscolus Quercifolias leaf extract were found to be dark green in colour, semi solid, and taste is acrid. Solubility testing of alcoholic extract of Cnidoscolus Quercifolias leaf is done mainly to study the ability of the dissolve in different solvent for the preparation of aqueous extract for dosing. The alcoholic extractwas observed to be dissolved in water and DMSO. In the present study, the preliminary phytochemicals test was done on the alcoholic extract of Cnidoscolus Quercifolias leaf and it is found to be rich in Carbohydrates, Proteins, Saponin, Flavonoids and Phenolic compound. For the determination of protective effect of Cnidoscolus Quercifolias leaf extract against paracetamol induced Hepatotoxicity, firstly level of GSH and SOD was checked. GSH and SOD level was tested in vehicle treated group after that Paracetamol treated group and then 200 mg/kg of plant extract along with Paracetamol treated group and after that 400 mg/kg of plant extract along with Paracetamol treated group

KEYWORDS: *Herbal, Extract, Medicine, Antioxidant, Phytochemicals.*

INTRODUCTION

Herbal medicine is the use of medicinal plants for prevention and treatment of diseases: it ranges from traditional and popular medicines of every country to the use of standardized and titrated herbal extracts. Generally cultural root ednessen during and widespread use in a Traditional Medical System may indicate safety, but not efficacy of treatments, especially in herbal medicine where tradition is almost completely based on remedies containing active principles at very low and ultra low concentrations, or relying on magical-energetic principles. In the age of globalization and of the so-called‘plateworld’,assessing the ‘transferability’ of treatments between different cultures is not a relevant goal for clinical research, while are the assessment of efficacy and safety that should be based on the regular patterns of mainstream clinical medicine. The other black box of herbal-based treatments is the lack of definite and complete information about the composition of extracts. Herbal derived remedies need a powerful and deep assessment of their pharmacological qualities and safety that actually can be realized by new biologic technologies like pharmacogenomic, metabolomic and microarray methodology. Because of the large and growing use of natural derived substances in all over the world, it is not wise to rely also on the tradition or supposed millenarian beliefs; explanatory and pragmatic studies are useful and should be considered complementary in the acquisition of reliable data both for health caregiver and patients. In recent times natural products are becoming an integral part of human health care system, because there is a now popular concern over toxicity and side effects of modern drugs. There is also a realization that natural medicines are safer and allopathic drugs are often ineffective in several aliments. Medicinal plants existed even before human being made their appearance on the earth. Man's existence on this earth has been made possible only because of the vital role played by plant kingdom in sustaining his life. Since the down of civilization, in addition to food crops, man cultivated herbs for his medicinal need.In the last few decades there has been an exponential growth in the filed of herbal medicine. It is getting popularized in developing and developed countries owing to its natural origin and lesser side effects. More than 700 mono and polyherbal

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preparations in the form of decoction, tincture, tablets and capsules from more than 100 plants are in clinical use .However, there are many limitations regarding safety and efficacy of these preparations. Knowledge about active principles of herbal preparations are not well defined, information on toxicity and adverse effect of these formulations are lacking.

Information regarding pharmacokinetics and bioavailability is not available. Packet inserts providing details regarding safety and warning are not required for sale of these, which are available as over the counter preparations. The lay public should know the risk of untested and unregulated remedies. Selection of plant material based on quality, standardization of methods of preparation, enforcement of regulation regarding appropriate labels are measures, which will improve the quality and acceptability of herbal preparations as therapeutic agents. Documentation of research publications in journals and availability of information on website, are other measures to assist research in this field.

Classification of Herbal Medicine System

Herbal Medicine can be broadly classified into various basic systems; Traditional Chinese Herbalism, which is part of Traditional Oriental Medicine, Ayurvedic Herbalism, which is derived from Ayurveda, and Western Herbalism, which originally came from Greece, Rome and Europe then spread to north and South America. Chinese and Ayurvedic Herbalism have developed into highly sophisticated system of diagnosis and treatment over the centuries. Western Herbalism is today primary a system of folk medicine etc.

Traditional system of medicine such as Ayurveda(India), Traditional Chinese Medicine(TCM), Tibetan Medicine, Unani-tibb (Greco-arabic) and Kampo (Japan) have a long and impressive history of effectiveness. Modern research has now confirmed the usefulness and safely of what has been used as primary medical care by much of the world's population.

Herbal and Alternative types of Medicine

Many people argue about the validity of natural and alternative types of medicine as effective medicines mainly due to the lack of scientific research performed to prove or disprove their effectiveness. Pharmaceutical companies are unable to patent herbal remedies as the wide spread use of natural and alternative types of medicine would basically put them out of business. (Patwardhan, 1992).

Need and Scope of Herbal Therapy

Today we are more concerned with life style diseases like depression, cancer and heart troubles caused by faulty nutrition and stress. Because these diseases have a mental or emotional component, there is a growing conviction that allopathy is largely unable to cure them, all of it offers is temporary relief from symptoms. There is a need of alternative therapy, to cover a good health for all. Herbal therapy will be one of the best practices to overcome the illness. Traditional Indian practice held that certain drugs should be formulated through the addition of chosen substance that enhances bioavailability of the drug. Recent work, particularly in two Indian modern biology labs, has confirmed this bioavailability enhancer ability of pepper and point to the active component as the molecule piperine. An anti-TB drug RIFAMPICIN has to be given at a higher dose than required, in order to compensate for losses on the way to the target site. Formulation of piperine with rifampicin will save the drug and counter effects.

Herbal oriented pharmaceutical companies like Dabur and the Himalaya Drug Company are investing crores of rupees on researching, developing and popularizing OTC remedies. Most of these address modern maladies such as stress, premenstrual syndrome, Depression and Obesity based on adapted version of ancient Vedic formulas (Thaibinh, 1998).

MATERIALS AND METHODS

Table 1: List of Instruments

S. No.	Instrument	Company
1	Vertex Shaker	Remi
2	Double Beam UV-VIS Spectrophotometer	Systronic
3	Cooling microcentrifuge	Remi
4	Clinical Centrifuge	Remi
5	High speed homogenizer	Remi
6	Animal weighing balance	Scientech
7	Syringe discarder	MRK Healthcare
8	Refrigerator	Godrej
9	Digital colony counter	EI
10	Digital camera	Sony

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Chemicals Used

Table 2: List of chemicals

S. No.	Chemical Name	Company
1.	Sodium Carbonate	Merck
2.	Ethylene Diamine Tetra Acetic Acid	Merck
3.	Acetic Acid	Merck
4.	Ammonia	Merck
5.	Pyridine	Merck
6.	Nitro-Bluetetrazolium	Himedia
7.	Nutrientbroth	Himedia
8.	Potassium Dehydrogenate Phosphate	Merck
9.	Dipotassium Hydrogen Phosphate	Himedia
10.	Agar-Agar	Himedia

METHODS

Selection and collection plant: Plant and plant parts was selected on the basis of Ethano-botanical survey.

Authentication of plant

The authentication of plant was done by the botanist. A herbarium of plants weresubmitted in Dept. of Botany Janata PG College, APS University and authenticated by Dr. S. N. Dwevedi Professor and Head Department of Botany Janata PG College, APS University, Rewa, M.P.

Extraction of plant material:

Cnidoscolus Quercifolias leaves collected, washed with distilled water. 250 gm dried *Cnidoscolus Quercifolias* leaves were ground to powder form and stored in a tightly sealed container. The Soxhlet apparatus and method was used for extraction.The Soxhlett himble was filled with the powdered leaves and inserted into the Soxhlet main chamber and closed. One liter of70% ethanol was filled into the Soxhlet main chamber and attached to the Soxhlet apparatus, which was heated until the solvent vapour filled the main chamber. The solvent vapour then condensed and dripped back down into the chamber containing the *Cnidoscolus Quercifolias* leaf extract. The *Cnidoscolus Quercifolias* leaf extract using 70% ethanol was then evaporated with a rotary evaporator at3 0oC and concentrated to50 Ml before beingfreeze-dried.The powdered form of freeze-dried extract was kept in the freezer to maintain the compound.

RESULT AND DISCUSSION

Table 3: Physical Evalution of Cnidoscolus Quercifolias leaf extract

S. No.	Organoleptic Characteristics	Result
1.	Colour	Dark Green
2.	Taste	Acrid
3.	Odour	Pungent
4.	Appearance	Semi-solid
5.	Consistency	Sticky

Solubility Tests

Table 4: Solubility of Cnidoscolus Quercifolias leaves extract in different solvents.

S.No.	Solvent	Observation
1.	DMSO	Soluble
2.	Distilledwater	Soluble
3.	Chloroform	Insoluble
4.	Methanol	Soluble

In-vitro antioxidant potential of hydroalcohalic Extract of *Cnidoscolus Quercifolias*

Total phenol and total flavonoid content:

Total phenolic content was measured using the Folin–Ciocalteu reagent in the extract and expressed as Gallic acid equivalent.

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Table 5: Total phenolic content and total flavonoid content of alcoholic extract

Extracts	Total Phenolic Content (mg of GAE/g)	Total Flavanoid Content (mg of QE/g)
Cnidoscolus Quercifolias	64.65± 1.2	46.43 ±1.32

Values represent mean ± SD (n=6)

2,2-diphenyl -1-picrylhydrazyl (DPPH) radical scavenging activity

Antioxidant activity of hydroalcohalic extract of *Cnidoscolus Quercifolias* was evaluated by various in-vitro methods. DPPH radical was used as a substrate to evaluate free radical scavenging activity of hydroalcoholic extract.

Table 6: DPPH radical scavenging activity of Cnidoscolus Quercifolias

Concentration µg/ml	% Inhibition	
	Ascorbic Acid	*CnidoscolusQuercifolias*
10	45.54±0.05	40.76±0.04
40	54.765±0.03	49.65±0.02
60	66.86±0.02	65.76±0.05
80	76.97±0.04	73.65±0.04
100	89.32±0.06	82.65±0.02

Values are expressed as mean ± SD (n=6). Values are significant at $p<0.05$.

Total flavonoid are expressed as mg of total flavonoid content/g of sample, where GAE = Gallic acid equivalent, QE = Quercetin equivalent

Nitric oxide scavenging activity

In the Nitric oxide scavenging assay, crude extract of the plant was evaluated for its inhibitory effect on nitric oxide production and ascorbic acid was used as standard.

Table 7: Nitric oxide scavenging activity of Cnidoscolus Quercifolias

Concentration µg/ml	**% Inhibition**	
	Ascorbic Acid	***CnidoscolusQuercifolias***
10	28.43±0.15	16.15±0.12
40	36.11±0.07	24.12±0.02
60	43.89±0.12	32.54±0.13
80	55.97±0.22	46.25±0.21
100	67.92±0.11	52.28±0.04

In vivo oxidative stress markers

Table 8: Effect of Cnidoscolus Quercifolias leaf extract on SOD in Paracetamol induced oxidative stress in Liver.

S. No.	Groups	Absorbance
1.	Control	151.83±11.64
2.	Vehicle	56.47±31.53
3.	Ex(200mg/kg)	78.36±28.92**
4.	Ex(400mg/kg)	111.02±22.52**

Significantly different ($P<0.05$) as compared to the SOD level in the normal control group. Results are expressed as Mean±SD

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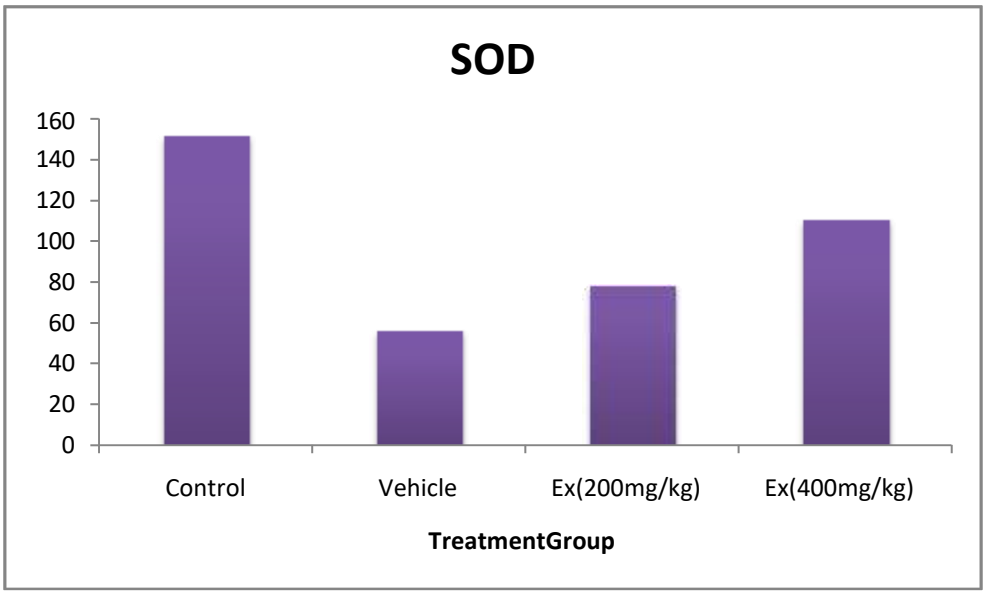

Figure 1: Effect of Cnidoscolus Quercifolias leaf extract on SOD in Paracetamol induced oxidative stress in Liver.

Table 9: Effect of Cnidoscolus Quercifolias leaf extract on GSHin Paracetamol induced oxidative stress in Liver

S. No.	Groups	Absorbance
1.	Control	0.4352±0.75
2.	Vehicle	0.26± 0.066
3.	Ex(200mg/kg)	0.32±0.052**
4.	Ex(400mg/kg)	0.466±0.028**

Significantly different (P<0.05) as compared to the GSH level in the normal control group. Results are expressed as Mean±SD.

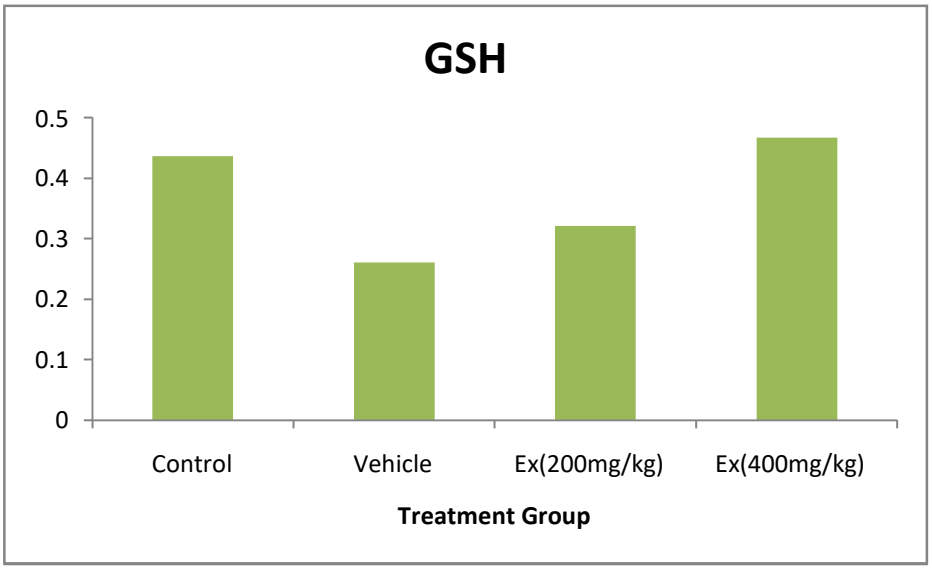

Figure 2: Effect of Cnidoscolus Quercifolias leaf extract on GSH in Paracetamol induced oxidatives tress in Liver

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Liver Function test

Table 10: AST (SGOT)

S. No.	Groups	Absorbance
1.	**Control**	78.33±1.366
2.	**Vehicle**	221.33±10.875
3.	**Ex(200mg/kg)**	271.83±9.087**
4.	**Ex(400mg/kg)**	106.17±4.708**

Significantly different (P<0.05) as compared to the SGOT level in the normal control group. Results are expressed as Mean±SD

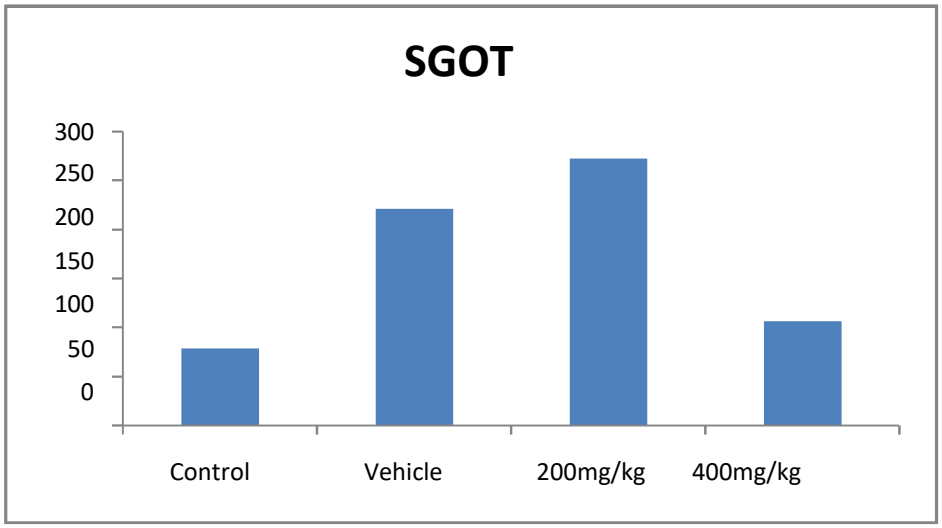

Figure 3: Effect of Cnidoscolus Quercifolias leaf extract on AST in Paracetamol induced Liver model

Table 11: ALT (SGPT)

S. No.	Groups	Absorbance
1.	**Control**	41.00±4.69
2.	**Vehicle**	162.83±8.424
3.	**Ex(200mg/kg)**	200.1±7.083**
4.	**Ex(400mg/kg)**	77.00±3.795**

Significantly different(P<0.05) as compared to the SGPT level in the normal control group. Results are expressed as Mean±SD

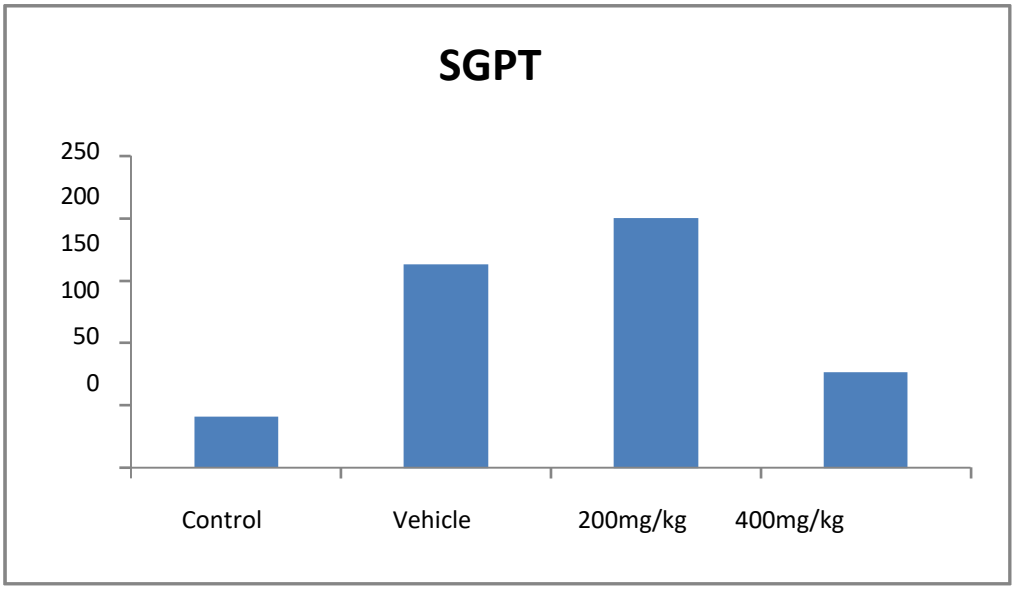

Figure 4: Effect of Cnidoscolus Quercifolias leaf extract on AlT inParacetamol induced Liver model.

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Table 12: ALP

S. No.	Groups	Absorbance
1.	**Control**	179.67±4.179
2.	**Vehicle**	306.83±4.708
3.	**Ex(200mg/kg)**	105.5±2.429**
4.	**Ex(400mg/kg)**	198.50±3.688**

Significantly different (P<0.05) as compared to the ALP level in the normal control group. Results are expressed as Mean±SD

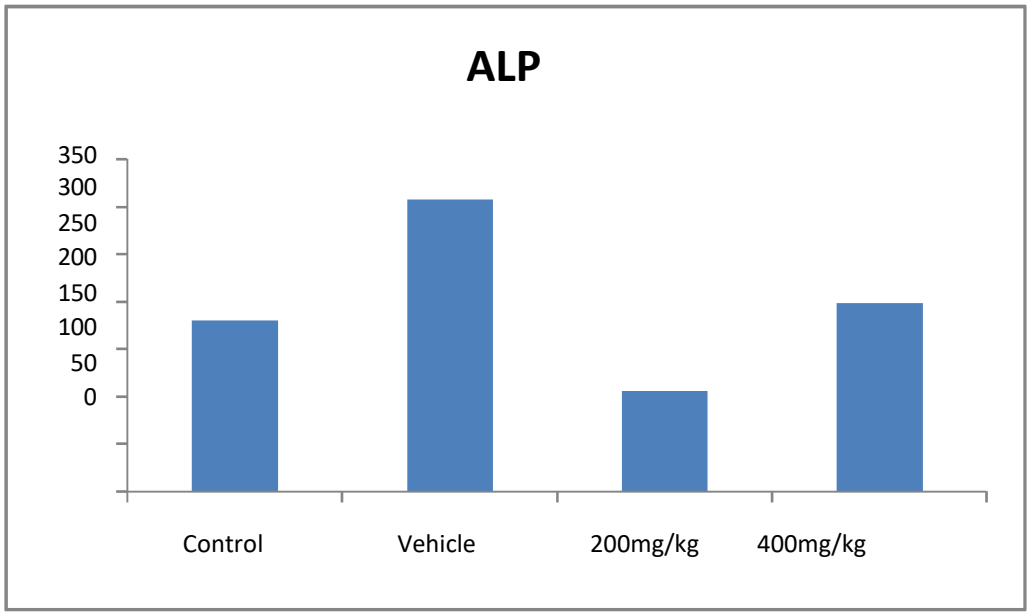

Figure 5: Effect of Cnidoscolus Quercifolias leaf extract on ALP in Paracetamol induced Liver model.

SUMMARY AND CONCLUSION

In present investigation one of traditionally used herbs anti-Hepatotoxicity being assessed against the Paracetamol induced Hepatotoxicity in rats.The drug related Hepatotoxicity is uncommon for many drugs, the reported incidence is between 1 in 10,000- its true incidence is difficult to determine. The number may be much higher,because of underreporting,difficulties in detection or diagnosis,and incomplete observation of persons exposed (Navarro and John, 2006). Paracetamol treatment caused significant ($p<0.001$) decreases in the activities of SOD, catalase, GPx and GSH level in liver tissue when compared to control group.. Silymarin-treated animals also showed a significant ($p<0.001$) increase in antioxidant enzymes, namely SOD, catalase, GPx activities and GSH level compared to paracetamol-treated rats.To understand the effect of the extract on liver, histology of liver was performed.

Firstly, Organoleptic Characterization of plant extract was performed. Organoleptic evaluations are subjective, sensory judgements. They can involve eyeing, feeling and taste of the extract to the judge its appearance, coour, integrity, texture and flavours. The organoleptic characters of alcoholic extract of *Cnidoscolus Quercifolias* leaf extract were found to be dark green in colour, semi solid, and taste is acrid. Solubility testing of alcoholic extract of *Cnidoscolus Quercifolias* leaf is done mainly to study the ability of the dissolve in different solvent for the preparation of aqueous extract for dosing. The alcoholic extractwas observed to be dissolved in water and DMSO. In the present study, the preliminary phytochemicals test was done on the alcoholic extract of *Cnidoscolus Quercifolias* leaf and it is found to be rich in Carbohydrates, Proteins, Saponin, Flavonoids and Phenolic compound. In present study Acute oral toxicity of plant extract was performed to check the toxicity of plant and extract was found to be non toxic up to the dose of 2000 mg/kg. Hence, 2000 mg/kg was considered as not observed adverse effect limit (NOAEL).$1/10^{th}$ and $1/5^{th}$ of NOAEL, i.e. 200mg/kg and 400mg/kg were selected as dose for oral administration of extract. For the determination of protective effect of *Cnidoscolus Quercifolias* leaf extract against paracetamol induced Hepatotoxicity, firstly level of GSH and SOD was checked. GSH and SOD level was tested in vehicle treated group after that Paracetamol treated group and then 200 mg/kg of plant extract along with Paracetamol treated group and after that 400 mg/kg of plant extract along with Paracetamol treated group. In-vivo antioxidant activity was measured through a set of enzymes including SGOT, SGPT, and ALP. The levels were measured and it indicated that the extract had significant antioxidant activity however the results obtained were

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dose dependent the higher the dose (400 mg/kg) the better activity. The extract administered at dose 400mg/kg showed better activity. In animal treated with Paracetamol level of **SGOT** was 222.00±31.166, which were significantly higher (P<0.001) as compared to vehicle treated animals. The amino transferases are the most frequently utilized and specific indicators of hepato cellular necrosis. these enzymes Aspartate aminotransferase (AST, formerly serum glutamate oxaloacetic transaminase-SGOT) catalyze the transfer of the amino acids of aspartate and alanine respectively to the keto group of ketoglutaric acid.AST is present in a wide variety of tissues like the heart, skeletal lmuscle, kidney, brain and liver.Large increases in mitochondrial AST occur in serum after extensive tissue necrosis. Because of this, assay of mitochondrial AST have been advocated in myocardial infarction. Mitochondrial AST is also increased in chronic liver diseases. In extract treated animals with 200mg/kg and 400mg/kg level of SGOT was found to be 106.25±4.349, 268.75±32.755 respectively which is significantly less (P<0.001) when compared with Paracetamol treated animals. In animals treated with Paracetamol level of **SGPT** was 163.50±10.376, which were significantly higher (P<0.001) as compared to vehicle treated animals. The amino transferases are the most frequently utilized and specific indicator of hepatocellular necrosis. these enzymes Aspartate aminotransferase (AST, formerly serum glutamateo xaloacetic transaminase-SGOT) catalyze the transfer of the amino acids of aspartate and alanine respectively to the keto group of ketoglutaric acid. ALT is primarily localized to the liver. (Nalpus et al., 1986). In extract treated group of animals with 200mg/kg and 400mg/kg level of SGPT was found to be 77.00±4.396, 199.50±11.818 respectively.

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