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A POSITIVE CONTROLLED, RANDOMISED CLINICAL TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF LIVOMYN IN THE TREATMENT OF NAFLD

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Abstract

Objectives: To evaluate the clinical efficacy and safety of Livomyn in NAFLD.

Material and Methods: A prospective, interventional clinical study was conducted on 300 patients of both sexes, aged between 18-65 years, confirmed with NAFLD from clinical examination, laboratory tests, ultrasound findings, and who were willing to give informed consent. All patients received Livomyn at a dose of 1 tablet thrice daily for 8 weeks. All patients were evaluated at baseline and 8 weeks for biochemical investigations [hs-CRP, TNF-α, NF-κB, ALT, and AST (IU/L)].

Observation: Livomyn after 8 weeks, reduced inflammatory biomarkers including hs-CRP from 6211.8 ± 4238.2to 5119.2 ± 4668.2; TNF-α from 21.27 ± 5.94to 18.16 ± 4.95 (<0.001) and NF-κB from 2.28 ± 1.13to 1.82 ± 0.69. Further Livomyn reduced elevated liver enzymes including ALT from 29.19 ± 17.01to 22.90 ± 11.09(<0.001) and AST from 19.56 ± 10.52 to 22.90 ± 11.09(<0.001) after 8 weeks of treatment. Livomyn significantly reduced Fibrosis from 7.68 ± 2.66 to 6.82 ± 2.62(<0.001) and Steatosis from 328.19 ± 32.45 to 310.92 ± 44.10. compared to the baseline. Similar reductions were also observed in the positive (Pioglitazone) controlled group. But none of the changes were significantly different between two groups.

Result: Livomyn produced a significant reduction comparable to the positive (Pioglitazone) controlled drug, in all the inflammatory/metabolic parameters associated with NAFLD

assessed after 8 weeks of treatment. No adverse events were reported by any patients. This indicates that Livomyn is clinically effective and safe for NAFLD.

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Introduction:-

Non-Alcoholic Fatty Liver Disease (NAFLD) has emerged as a significant health concern in recent years, particularly among individuals with obesity and those with type 2 diabetes mellitus. In India, liver diseases are becoming increasingly important public health issues, adding considerably to the global health burden. Since 1980, there has been a notable rise in chronic liver diseases, including cirrhosis, in India, diverging from trends observed in other Asian nations such as China. However, the accuracy of data and consistency in reporting standards pose challenges, affecting the quality of epidemiological insights.

Despite these challenges, evidence indicates a growing economic and healthcare impact from liver diseases. The shift towards a more Westernized diet and sedentary lifestyle is contributing to a rise in both alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD), alongside traditional viral causes.

Pathogenesis

The development of NAFLD involves a multifaceted process, beginning with free fatty acid (FFA) toxicity and triglyceride accumulation. This process is further complicated by inadequate hepatocyte proliferation, which acts as a 'third hit'. Non-alcoholic fatty liver disease (NAFLD) starts with the accumulation of hepatic fat from various sources such as adipose tissue, diet, and de novo lipogenesis, impacting processes related to fat synthesis, delivery, export, and oxidation. Key factors like insulin resistance and genetic predispositions play significant roles in advancing NASH. Additionally, mitochondrial dysfunction and oxidative stress are central to the pathophysiology of NAFLD and NASH. A thorough understanding of these intricate mechanisms is crucial for devising targeted treatment strategies and effective management approaches for both NAFLD and NASH.

Conventional Treatment

Current treatments for Hepatitis primarily focus on improving the metabolic factors contributing to the disease. These approaches include weight loss, regular exercise, reducing insulin resistance (IR), and improving diabetic control. Recommended lifestyle changes involve dietary modifications and increased physical activity. Medical treatments may involve insulin sensitizers like metformin and thiazolidinedione, weight loss medications such as orlistat and sibutramine, and, for severely obese patients, bariatric surgery. For end-stage cirrhosis, liver transplantation remains the only curative option. Research is ongoing to develop targeted therapies that could reverse or prevent the progression to more severe stages like Non-Alcoholic Steatohepatitis (NASH) and fibrosis, which are critical for predicting liver-related complications.

Currently, no pharmacological agents have received official approval for NAFLD treatment. The standard intervention involves lifestyle modifications, including caloric restriction and increased physical activity. These changes can lead to weight loss, which may improve liver pathology and reduce hepatic fat accumulation. Some pharmacological options, such as antioxidants, insulin sensitizers, and lipid-lowering drugs, are also suggested.

Despite advancements in conventional medicine, herbal remedies remain appealing due to their natural origins and ease of access. Traditionally used around the world for liver health, herbal medicines have recently shown promise in the management of NAFLD. They are considered valuable sources of bioactive compounds that can enhance liver function.[i]

The present study investigates Livomyn, a polyherbal formulation developed by Charak Pharma Pvt. Ltd., for its efficacy and safety in treating NAFLD. This formulation has been standardized through established procedures and has undergone an acute toxicity study.

Materials and Method:-

Study Design:

Positive Controlled, Randomised Clinical Trial

Study Objectives:

Primary:

The main objective of the study was to compare and evaluate the clinical efficacy of Livomyn against Pioglitazone in NAFLD. Further, the study also observed the clinical safety of Livomyn in NAFLD.

Secondary:

To evaluate the reduction of serum TNF-α, hs-CRP concentration, and NF-kB activity in peripheral blood mononuclear cells PBMCs by Livomyn.

Inclusion Criteria:

Patients who visited the outpatient department and were diagnosed with non-alcoholic fatty liver disease (NAFLD) by the attending gastroenterologist were included in the study. These patients may have undergone confirmatory diagnostic procedures, such as ultrasound imaging, and had abnormal liver function tests indicating liver injury or inflammation, such as elevated alanine amino transferase (ALT) or aspartate aminotransferase (AST) levels. The study also included individuals with a previous diagnosis of NAFLD. Eligible participants were between 18 and 65 years old and exhibited NAFLD symptoms, including weakness, loss of appetite, nausea, jaundice, itching, and fluid retention or swelling in the legs and abdomen.

Exclusion Criteria:

Patients were excluded from the study if they had significant alcohol consumption, were pregnant or breastfeeding, had malignancies, or suffered from other liver, cardiovascular, respiratory, or kidney diseases. Additionally, those on medications known to induce hepatic steatosis or liver injury, or with serious medical conditions that could interfere with study outcomes or increase the risk of complications, were excluded. Patients who were unable or unwilling to provide informed consent or adhere to study procedures and follow-up assessments were also excluded.

Study Design:

A randomized phase 3, positive controlled clinical trial in 240 patients diagnosed with NAFLD was planned following required GCP guidelines. After careful selection in terms of the eligibility criteria, screened subjects willing to enrol after explaining the clinical study procedure were requested to sign the Patient Consent Form. Eligible participants were randomly assigned to receive either Livomyn or Piaglitazone TID (3 times a day) after each meal for 8 weeks. Randomization lists were computer-based by a statistician and the participants and project managers were completely unaware (blind) about the intervention and control groups. At baseline visit at 0 weeks, Patient information sheet was provided to each subject in their language of preference. Case record form (CRF) was filled by the attending physician with complete medical history and required personal details of the subject at the start of the study. Copies of any medical reports of the subject or investigational procedure results related to the condition such as blood profile, radio-imaging techniques were procured along with the CRF.

Clinical assessments

At both the start and end of the study, we measured participants' weight, height, and waist circumference. Weight was recorded with a digital scale accurate to 100 grams, with participants in minimal clothing and without shoes.

Height was measured with a tape measure to the nearest 0.5 cm, while participants stood normally and without shoes. Body mass index (BMI) was calculated by dividing weight (in kilograms) by the square of height (in meters). To ensure consistency and minimize error, all measurements were taken by the same person.

After a 12-hour fast, blood samples for biochemical analysis were collected at the beginning and end of week 8, following standard protocol. All biochemical tests were conducted in the same laboratory. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were measured using enzymatic methods, while TNF-α and high-sensitivity C-reactive protein (hs-CRP) concentrations were determined with an enzyme-linked immunosorbent assay (ELISA) kit. NF-κB p65 levels in peripheral blood mononuclear cells (PBMCs) were assessed according to the manufacturer's protocol. At the entry and the end of study, hepatic fibrosis and steatosis were evaluated using Fibroscan. This assay was performed by the same operator who was blinded to the study randomization. Additionally, participants' physical activity was evaluated using the metabolic equivalent of task (MET) questionnaire.

Intervention:

The efficacy and safety of Livomyn, a polyherbal formulation produced by Charak Pharma Pvt. Ltd., were investigated in patients with non-alcoholic fatty liver disease (NAFLD). The treatment involved administering one tablet three times daily after meals with water for a duration of 8 weeks. Each Livomyn tablet contains a blend of herbs including Bhuiamla, Triphala, Punarnava, Rohitak, Ardusi, Bhangra, Sonth, Giloy, Dhania, Kalmegh, and Katuki. Patient evaluations were conducted at baseline, and at 4 and 8 weeks after starting the treatment. Efficacy was assessed by monitoring improvement in laboratory parameters.

Observation:-

Table 1:- Shows the Baseline characteristics of patients with NAFLD who participated in our study before intervention.

Table 1

Variables		**Control group**	**Livomyn group**	**P value**
Age (year)		10.9 ± 45.13	11.5 ± 46.19	0.473
Sex [male, n,(%)]		62 (51.67%)	48 (48.3%)	0.407
Physical Activity (MET.h.d)		4.63 ± 32.03	3.65 ± 32.69	0.592
Smoking	Yes (Smoker or Ex-smoker)	21 (17.5%)	5 (4.1%)	0.167
	No (Never smoked)	99 (82.5%)	115 (95.8%)	
Weight (kilogram)		89.22 ± 13.05	85.02 ± 11.16	0.225
BMI (kg/m^2)		32.38 ± 5.02	32.30 ± 4.55	0.956
Waist circumference (cm)		103.28 ± 8.83	102.19 ± 8.78	0.948
Total energy (kcal)		2323.01 ± 540.59	2355.41 ± 703.69	0.858
hs-CRP (ng/dL)		6705.05 ± 4797.9	5647.15 ± 3858.4	0.412
TNF-α (pg/mL)		18.63 ± 2.2	19.34 ± 5.4	0.610
NF-κB		2.13 ± 0.92	2.07 ± 1.03	0.842
Fibrosis grade (kPa)		6.52 ± 2.38	6.98 ± 2.42	0.132
Steatosis grade (db/m)		315.18 ± 35.69	298.35 ± 29.5	0.218

Table 2:- Shows Inflammatory biomarkers and hepatic characteristic changes after 8weeks of intervention.

Table 2						
Characteristic	**Group**	**Baseline**	**After 8 weeks**	**P [a]**	**Change (%)**	**P [b]**
hs-CRP (ng/dL)	Livomyn	6211.8 ± 4238.2	5119.2 ± 4668.2	0.12	−1092.6 ± 423.9	0.660
	Control	7375.5 ± 5274.4	5841.2 ± 5578.9	0.53	−1534.3 ± 304.5	
TNF-α (pg/mL)	Livomyn	21.27 ± 5.94	18.16 ± 4.95	<0.001	−3.11 ± 1.0	0.972
	Control	20.49 ± 2.42	18.19 ± 2.31	0.02	−2.30 ± 0.11	
NF-κB	Livomyn	2.28 ± 1.13	1.82 ± 0.69	0.044	−0.46 ± 0.30	0.539
	Control	2.34 ± 1.01	2.23 ± 0.56	0.209	−0.11 ± 0.21	
ALT (IU/L)	Livomyn	29.19 ± 17.01	22.90 ± 11.09	<0.001	−6.29 ± 16.06	0.778
	Control	30.82 ± 14.37	23.32 ± 8.49	<0.001	−7.50 ± 17.38	
AST (IU/L)	Livomyn	19.56 ± 10.52	16.23 ± 8.20	<0.001	−3.33 ± 8.29	0.728
	Control	17.85 ± 6.23	14.05 ± 4.46	<0.001	−3.80 ± 5.89	
Fibrosis (kPa)	Livomyn	7.68 ± 2.66	6.82 ± 2.62	<0.001	−0.86 ± 0.92	0.364
	Control	7.17 ± 2.62	6.62 ± 1.98	0.095	−0.55 ± 1.27	
Steatosis (db/m)	Livomyn	328.19 ± 32.45	310.92 ± 44.10	0.015	−17.27 ± 33.79	0.112
	Control	346.70 ± 39.26	311.50 ± 54.81	0.001	−35.20 ± 37.73	

Table 3:- Shows physical activity of participants evaluated using the metabolic equivalent of task (MET) questionnaire.

Table 3						
Activity	**Group**	**Time Point**	**Avg. Duration (mins/week)**	**MET Value**	**Average MET-hours/week**	**SD (MET-hours)**
Sitting	Livomyn	Before Intervention	400	1	6.7	1.3
	Livomyn	After Intervention	380	1	6.3	1.2
	Control	Before Intervention	410	1	6.8	1.2
	Control	After Intervention	390	1	6.5	1.3
Light Walking	Livomyn	Before Intervention	170	3	8.5	2.1
	Livomyn	After Intervention	180	3	9.0	2.0
	Control	Before Intervention	175	3	8.8	2.0
	Control	After Intervention	185	3	9.2	2.1
Moderate Walking	Livomyn	Before Intervention	110	5	9.2	2.4
	Livomyn	After Intervention	120	5	10.0	2.5
	Control	Before Intervention	115	5	9.6	2.5
	Control	After Intervention	125	5	10.4	2.6
Vigorous Exercise	Livomyn	Before Intervention	70	8	9.3	3.1
	Livomyn	After Intervention	65	8	8.7	2.9
	Control	Before Intervention	72	8	9.6	3.2
	Control	After Intervention	68	8	9.0	3.1
Household Chores	Livomyn	Before Intervention	160	4	10.7	2.2
	Livomyn	After Intervention	155	4	10.3	2.1
	Control	Before Intervention	165	4	11.0	2.4
	Control	After Intervention	160	4	10.7	2.3
Cycling	Livomyn	Before Intervention	80	6	8.0	2.4
	Livomyn	After Intervention	85	6	8.5	2.5

	Control	Before Intervention	82	6	8.2	2.5
	Control	After Intervention	88	6	8.8	2.6

Results:-

A total of 240 patients were enrolled and completed the study within the designated timeframe. Livomyn was found to be safe and well-tolerated comparable to the same of control drug, with no adverse effects reported by any participants. At baseline, there were no significant differences in demographic data between the Livomyn and control groups. Both groups demonstarted significant decrease in the weight, BMI, waist circumference (Table 1) and increase in physical activity (Table 3). However, there was no significant difference between two groups.

Livomyn after 8 weeks, reduced inflammatory biomarkers including hs-CRP from 6211.8 ± 4238.2to 5119.2 ± 4668.2; TNF-α from 21.27 ± 5.94 to 18.16 ± 4.95 (<0.001) and NF-κB from 2.28 ± 1.13 to 1.82 ± 0.69. Further Livomyn reduced elevated liver enzymes including ALT from 29.19 ± 17.01 to 22.90 ± 11.09 (<0.001) and AST from 19.56 ± 10.52 to 22.90 ± 11.09 (<0.001) after 8 weeks of treatment. Livomyn significantly reduced Fibrosis from 7.68 ± 2.66 to 6.82 ± 2.62 (<0.001) and Steatosis from 328.19 ± 32.45 to 310.92 ± 44.10. compared to the baseline. Similar reductions were also observed in the positive (Pioglitazone) controlled group.

Additionally, no significant differences were observed between the two groups in serum levels of TNF-α, hs-CRP, and NF-κB, as well as in hepatic characteristics. Baseline demographic and metabolic factors are detailed in Table 2. Livomyn supplementation led to a significant reduction in hepatic fibrosis ($p < 0.001$) and NF-κB activity in PBMCs ($p < 0.05$) compared to baseline (Table 2). Both groups showed a reduction in serum hs-CRP levels (Table 2). After 8 weeks of intervention, both groups experienced significant reductions in hepatic steatosis, as well as in serum levels of ALT, AST, and TNF-α (Table 2). However, there were no significant differences between the two groups in the extent of these changes (Table 2).

Discussion: -

Non-alcoholic fatty liver disease (NAFLD) encompasses a range of metabolic conditions, from simple liver fat accumulation (hepatic steatosis) to more severe stages involving inflammation, fibrosis, and cirrhosis. Currently, there are no specific drugs approved for treating NAFLD or its advanced form, non-alcoholic steatohepatitis (NASH). Existing treatments primarily focus on managing related conditions such as obesity, hyperlipidemia, insulin resistance, and type 2 diabetes mellitus. Guidelines recommend using any prescribed medications for NAFLD as off-label treatments, with efficacy and safety carefully monitored. Despite the limitations of current treatments, there is hope for the development of innovative, effective, and safe management options for the disease.[ii]

Research into bioactive compounds in foods has emerged as a promising strategy to address the challenges associated with lifestyle modifications. Several natural compounds have shown potential benefits in the cellular mechanisms related to NAFLD onset and progression.[iii]

Phyllanthus niruri contains ellagic acid and phyllanthin, which have demonstrated hepatoprotective effects against NAFLD. This compound significantly reduces liver enlargement, visceral fat, NAFLD score, fibrosis, and various biomarkers such as total cholesterol, LDL, free fatty acids, ALT, ALP, insulin levels, and insulin resistance. It also improves atherogenic ratios and reduces hepatic cholesterol, triglycerides, and malondialdehyde. Additionally, it inhibits α-glucosidase and pancreatic lipase enzymes and cholesterol micellization.[iv]

Andrographis paniculata improves hepatic steatosis by enhancing glucose tolerance and insulin sensitivity, and by reducing hyperinsulinemia, hyperglycemia, and hyperlipidemia.[v] It also regulates inflammation through the NF-κB pathway and reduces fatty acid uptake mediated by FATP2, thereby preventing hepatic damage.[vi]

Boerhavia diffusa, with its compound boeravinone B, helps alleviate gut dysbiosis and supports liver health, aligning with its traditional use as a functional food.[vii]

Picrorhiza kurroa counters hepatic lipid accumulation by decreasing fatty acid buildup, oxidative stress, and mitochondrial dysfunction in HepG2 cells. It reduces levels of reduces γ-Glutamyl Transpeptidase (GGT), Lactate Dehydrogenase (LDH), Alanine Amino-Transferase (ALT), Aspartate Amino-Transferase (AST) & Alkaline Phosphatase (ALP) levels, and downregulates inflammatory markers such as NF-kB, COX-2, IL-1β, and IL-6.[viii]

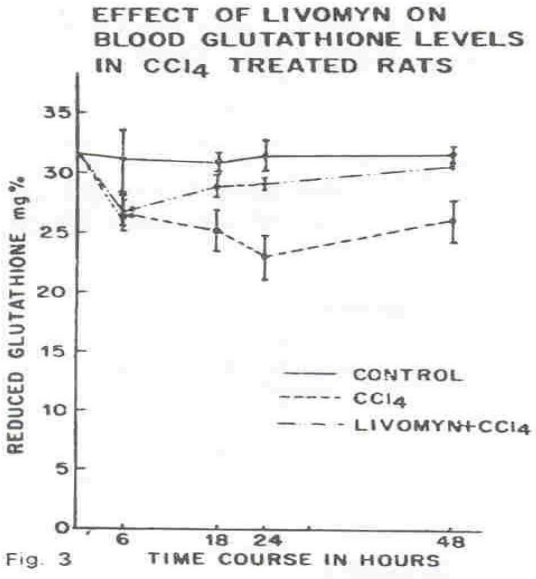

Fig. 3. Graphical representation of the effect of carbon tetrachloride alone and C Cl_4 along with Livomyn on blood glutathione concentrations in rats.

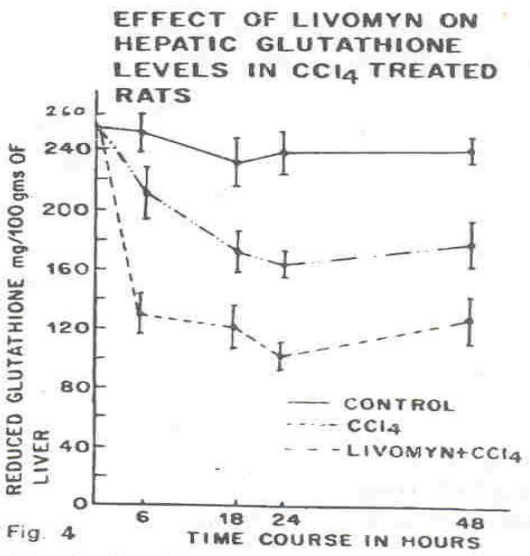

Fig. 4. Graphical representation of the effect of placebo (Solvent), carbon tetrachloride, and Livomyn plus carbon tetrachloride on the hepatic glutathione levels.

Previous studies have investigated the efficacy of Livomyn. Itshepato protective effect was evaluated against ethanol, CCl4 and galactosamine induced hepatotoxicity in Wistar rats. The evaluation of blood serum parameters exhibits significant reduction in the levels of bilirubin, SGOT, SGPT, LPO, alkaline phosphate and cholesterol whereas significant increase in Total protein and reduced GSH levels in Livomyn treated groups. The hepatoprotective effect was attributed to synergistic effect of potent antioxidant and hepatoprotective property of various medicinal plant extracts in Livomyn formulation.[ix]

Another controlled toxicity study, was carried out to investigate the protective action (GSH levels) of Livomyn against Carbom tetrachloride (CCl4) induced hepatic damage in experimental rats. CCl4 produced severe biochemical and histopathological changes in liver. However, the group of rats pretreated with Livomyn showed considerably higher levels of GSH as compared to the group receiving CCl4 alone.[x]

A comparative evaluation of Livomyn against a virustatic drug Ribavirin and placebo in management of Hepatitis revealed Livomyn showed both clinical and pathological cure marked by symptomatic relief, improved clinical status and progressive decline in serum biochemistry i.e. Bilirubin and transaminase in all the patients irrespective of their diseases status, whereas none of either on virustatic drug Ribavirin or Placebo had any clinico-pathological cure in 21 days therapy. Though decline in mean serum biochemistry was noted without reverting the serum bio-chemistry to normal. The study further noted that Livomyn can be prescribed to all without any restriction compred to virustatic drug Ribavirin, which cannot be prescribed to all. No untoward effect was noted in any of the patient. This study affirmed superiority of Livomyn over the virustatic Ribavirin in management of even viral hepatitis of either origin without any contra-indication or untoward effects.[xi]

A phase 4 study in 884 cases assessed by 115 clinicians reported efficacy of Livomyn Tablets in Acute Viral Hepatitis. Livomyn in the dose of 2 tablets thrice daily in adults or half of it in children for a maximum duration of 6weeks was employed to treat acute viral hepatitis in884 patients. The patients were followed up at 2,3,4,5and 6 weeks of therapy. There were 576 males and308 females. Amelioration of signs/symptoms and improvements in serum bilirubin as well as ALT levels were the criteria for efficacy. Haemoglobin concentration was also measured simultaneously during each patient visit. There was a progressive reduction in serum bilirubin and ALT levels levels at each follow-up and an analysis of these values versus the type of response likewise corroborated a similar trend as for serum bilirubin i.e. a statistically significant decrease in first three categories of response. There was a progressive and significant increase in haemoglobin concentration during each follow-up as a consequence of treatment. The outcome of therapy was categorized into 5 types of response: Excellent, Good, Fair, No change, or Worse. The patients started responding as early as 2 weeks after therapy. A vast majority of patients responded favourably. Excellent response was achieved in 39.5%, and a good response in 40.16%. This means that almost 80% of all the patients responded well. Livomyn proved to be highly effective and safe in the treatment of acute viral hepatitis over a period of 2 to 6 weeks.[xii]

Therefore, it is observed that the ingredients of Livomyn modulate metabolic factors associated with NAFLD. In a recent study, an 8-week treatment with Livomyn, a formulation containing these beneficial ingredients, led to significant improvements in all evaluated parameters. These findings suggest that Livomyn is both safe and effective in managing NAFLD and its associated metabolic disturbances.

Conclusion:-

The present interventional study indicates that Livomyn, a polyherbal formulation is effective and safe in controlling the signs and symptoms of NAFLD and its associated complications. There were no clinically significant adverse events either reported or observed during the entire study period. The overall compliance with the treatment was good and no treatment discontinuations were reported. Livomyn typically target metabolic pathways, insulin resistance, hepatocyte death, inflammatory cell recruitment or activation, and the gut-liver axis. Livomyn aims at reverting pathogenic liver metabolism with an alternative approach to disconnect the injury from inflammation and fibrosis also beneficial in viral, drug and alcohol induced hepatitis.

Cost of Study

All medications required during the 3 months of trial were provided by the sponsor. Radio-imaging and biochemical test mentioned were performed at the base line and the end of the trial. The cost for the same was sponsored by the company. Charak Pharma Pvt. Ltd. reserves all rights over any publications of the study during the course and post completion.

Conflict of Interest

To avoid any conflict of interest, study was carried out under the unbiased supervision of Dhanwantari hospital HCP who are not associated with the sponsors.

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