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A PROSPECTIVE, OPEN-LABEL, NON-RANDOMISED CLINICAL TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF LIVOMYN IN THE TREATMENT OFNAFLD

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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 50 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,4 weeks, 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 5647.1 ± 3858.4 to 4653.8 ± 4243.8; TNF-α from 19.34 ± 5.4 to 16.51 ± 4.5 (<0.001) and NF-κB from 2.07 ± 1.03 to 1.65 ± 0.63. Further Livomyn reduced elevated liver enzymes including ALT from 26.54 ± 15.46 to 20.82 ± 10.09 (<0.001) and AST from 17.78 ± 9.56 to 14.75 ± 7.45 (<0.001) after 8 weeks of treatment.

Result: Livomyn produced a significant reduction in all the inflammatory/metabolic parameters associated with NAFLD assessed after 8 weeks of treatment. In addition, a significant improvement in Clinical Global Impression in efficacy and tolerability was also observed. No adverse events were reported by any patients. This indicates that Livomyn is clinically effective and safe for NAFLD.

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Introduction:-

As a major health problem, Non-Alcoholic Fatty Liver Disease (NAFLD) has attracted attention over the past few years with high prevalence observed in obese individuals and even more in type 2 diabetes mellitus patients. In India, liver diseases are emerging as critical public health concerns, contributing significantly to the global burden. The prevalence of chronic liver diseases, including cirrhosis, has been on the rise since 1980, contrasting with trends in

other Asian countries like China. However, India faces challenges in data accuracy and uniform reporting standards, limiting the quality of epidemiological information available.

Despite these limitations, there is ample evidence pointing to the growing impact of liver diseases on both the economy and the healthcare system. The changing cultural and lifestyle landscape, characterized by a shift towards a more Westernized diet and sedentary habits, is fostering a rise in alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) alongside viral causes.

Pathogenesis

The pathogenesis of non-alcoholic steatohepatitis (NASH) involves free fatty acid (FFA) toxicity, triglyceride accumulation, and inadequate hepatocyte proliferation as a 'third hit'. Non- alcoholic fatty liver disease (NAFLD) originates from hepatic fat buildup due to various sourceslike adipose tissue, diet, and de novo lipogenesis, affecting fat synthesis, delivery, export, and oxidation. Insulin resistance and genetic factors significantly impact NASH progression. Furthermore, mitochondrial dysfunction and oxidative stress are fundamental mechanisms in the pathophysiology of NAFLD/NASH. Understanding these complex mechanisms is paramountfor developing targeted treatment strategies and effective management approaches for NAFLD and NASH.

Conventional Treatment

The current therapies for Non-Alcoholic Fatty Liver Disease (NAFLD) are centered around improving metabolic parameters contributing to disease pathogenesis, including weight loss, exercise, reducing insulin resistance (IR), and enhancing diabetic control. Lifestyle changes such as weight loss and exercise are recommended, while medical interventions include insulinsensitizers like metformin and thiazolidinedione, weight loss drugs such as orlistat and sibutramine, and bariatric surgery for morbidly obese patients. Liver transplantation remains the only curative option for end-stage cirrhosis. Research in this area focuses on developing targeted treatments to reverse or prevent the progression to more advanced stages like Non-Alcoholic Steatohepatitis (NASH) and fibrosis, which are crucial in predicting liver-related complications.

Currently, there are no pharmacological agents that are being officially approved in NAFLD therapy. The recommended intervention in NAFLD is lifestyle modification including energy intake restriction and physical activity enhancement. Lifestyle modification can reduce body weight and a moderate decrease of body weight could improve hepatic pathologic syndrome and decrease hepatic fat accumulation. Some pharmacological interventions classified as antioxidants, insulin sensitizers, and lipid-lowering drugs have been also recommended.

Although with the advances in conventional medicine, herbal medicines are easily accessible and do not require artificial synthesis, thus herbal medicine seems highly attractive for the effective management of NAFLD. Herbal medicines have been traditionally used in different countries of the world to improve liver conditions. In recent years, progress in drug development of NAFLD has been found in major advances with herbal medicines which are regarded as abundant sources of natural bioactive chemicals that improve hepatic functions.[1]

In the present study, Livomyn, a polyherbal formulation, manufactured by Charak Pharma Pvt.Ltd. was studied for its efficacy and safety in patients with NAFLD. The formulation has been standardized after formulating SOPs along with an acute toxicity study.

Materials and Method:-

Study Design:

Prospective, open-label, Non-randomised clinical trial.

Study Objectives:

Primary:

The main objective of the study was to evaluate the clinical efficacy of Livomyn inNAFLD. 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 activityin peripheral blood mononuclear cells PBMCs by Livomyn.

Inclusion Criteria:

Patients visiting the outpatient department, diagnosed by the attending Gastroenterologist with NAFLD who may have undergone any radio-imaging confirmatory diagnostic procedure (USG), with abnormal liver function tests, such as elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST), to confirm liver injury or inflammation associated with NAFLD or having previous diagnosis for the same were included. Patients below the age of 65 and above the age of 18 years, experiencing NAFLD symptoms like weakness, loss of appetite, nausea, jaundice, itching, fluid build-up and swelling in the legs and abdomen; with a documented diagnosis of NAFLD were included.

Exclusion Criteria:
Patients with significant alcohol consumption, pregnancy or breastfeeding mothers, suffering from malignancies, other liver, cardiovascular, respiratory and kidney diseases, who are taking medications known to cause hepatic steatosis or liver injury, with serious medical conditions that could confound study outcomes or increase the risk of complications during the study period, who are unable or unwilling to provide informed consent or comply with studyprocedures and follow-up assessments were excluded.

Study Design:
A non-randomized phase 4, prospective open label clinical trial in 50 patients diagnosed with NAFLD was planned following required GCP guidelines. Institutional Ethics Committee approvalfor the clinical trial was obtained before starting the study. 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. 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 reportsof 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 Weight, height, and waist circumference were measured for all participants at the baseline andthe end of the study. Measurement of weight with 100 g accuracy using the digital scale for participants wearing minimal clothing and no shoes and height with 0.5 cm accuracy using a tape measure while the participants were standing in a normal position with no shoes was carried out. Body mass index (BMI) was calculated as weight (in kilograms) divided by the square of height (in meters). To avoid measurement error, all measurements were accomplished by the same person. After 12 h fasting, for standard protocol, blood samples forbiochemical parameters were collected at the beginning and end of week 8. All biochemical tests were precisely assessed in the same laboratory. Serum concentration of alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were assessed using enzymatic methods. The concentration of TNF-α and high-sensitivity C-reactive protein (hs-CRP) concentration was measured using an enzyme-linked immunosorbent assay (ELISA) kit. NF-κBp65 was measured in peripheral blood mononuclear cells (PBMCs) nuclear extracts, according to the manufacturer's protocol. Moreover, the physical activity of participants was evaluated using the metabolic equivalent of task (MET) questionnaire.

Intervention:
Livomyn, a polyherbal formulation, manufactured by Charak Pharma Pvt. Ltd. was studied for its efficacy and safety in patients with NAFLD, in a dose of 1 tablet thrice a day after meals withwater were started for 8 weeks. Livomyn tablets contains Bhuiamla, Triphala, Punarnava, Rohitak, Ardusi, Bhangra, Sonth, Giloy, Dhania, Kalmegh and Katuki. The patients were evaluated at baseline, 4 weeks & 8 weeks after onset of treatment. Efficacy was measured in terms of reduction in abdominal pain and laboratory parameters and ultrasonography.

Observation:-

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

Table 1

Characteristics		Baseline	P value
Age (year)		11.5 ± 46.19	0.473
Sex (male, n,(%))		13 (48.1%)	0.407
Physical Activity (MET.h.d)		3.65 ± 32.69	0.592
Smoking	Yes (Smoker or Ex-smoker)	1 (4%)	0.167
	No (Never smoked)	26 (96%)	
Weight (kilogram)		85.02 ± 11.16	0.225
BMI (kg/m2)		32.30 ± 4.55	0.956
Waist circumference (cm)		102.19 ± 8.78	0.948

Total energy (kcal)	2355.41 ± 703.69	0.858
hs-CRP (ng/dL)	5647.15 ± 3858.4	0.412
TNF-α (pg/mL)	19.34 ± 5.4	0.610
NF-κB	2.07 ± 1.03	0.842

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

Table 2			
Inflammatory biomarkers	Baseline	After 8 weeks	P
hs-CRP (ng/dL)	5647.1 ± 3858.4	4653.8 ± 4243.8	0.12
TNF-α (pg/mL)	19.34 ± 5.4	16.51 ± 4.5	<0.001
NF-κB	2.07 ± 1.03	1.65 ± 0.63	0.044
ALT (IU/L)	26.54 ± 15.46	20.82 ± 10.09	< 0.001
AST (IU/L)	17.78 ± 9.56	14.75 ± 7.45	< 0.001

Results:-

Fifty patients were enrolled in this study. Only 1 patient (2%) dropped out due to being not interested in continuing the study. A total of 49 patients completed the study in the specified period of study. Livomyn was safe and well tolerated and none of the participants reported any adverse effects. Baseline values of demographic and metabolic factors are shown in Table 2. Livomyn was associated with a significant decrease in the activity of NF-κB in PBMCs ($p < 0.05$)as compared with the baseline. After treatment with Livomyn serum level of hs-CRP was reduced but this reduction was not significant ($p > 0.05$). Serum levels of ALT, AST, and TNF-α reduced significantly after 8 weeks of the study intervention.

Discussion:-

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of metabolic disorders ranging from a simple accumulation of excess triglycerides in the liver (hepatic steatosis) to hepatic steatosis with inflammation, fibrosis, and cirrhosis. Currently, no drugs are approved for the treatment of NAFLD and NASH and existing pharmacotherapy aims at the management of inter-current diseases such as obesity, hyperlipidemia, insulin resistance, and type 2 diabetes mellitus. All guidelines acknowledge that any medicines prescribed for NAFLD treatment should be considered as an off-label treatment and that their efficacy and safety should be carefully monitored. Although current pharmacotherapy may seem limited and of questionable efficacy,there is optimism that innovative safe, and effective options for the management of the disease will be made available shortly.[2] Studies of food bioactive compounds became an attractive approach to overcome the unwillingness toward lifestyle changes. Several natural compounds have been shown to exert beneficial effects in the cellular mechanisms involved in the onset and progression of NAFLD.[3]

Phyllanthus niruri with Ellagic acid and phyllanthin identified as major compounds could be further developed as a novel natural hepatoprotective agent against NAFLD. It is well documented to possess an inhibitory effect against NAFLD progression. It significantly reduces hepatomegaly, visceral fat weight; NAFLD score, fibrosis, and serum total cholesterol, low- density lipoprotein (LDL), free fatty acids (FFAs), alanine aminotransferase (ALT), alkaline phosphatase (ALP), insulin concentration, homeostatic model assessment of insulin resistance (HOMA-IR), serum atherogenic ratios TC/high-density lipoprotein (HDL), LDL/HDL (66%) and (TC–HDL)/HDL, hepatic content of cholesterol (43%), triglyceride and malondialdehyde (MDA). Further, it inhibits α-glucosidase, pancreatic lipase enzymes, and cholesterol micellization.[4]

Andrographis paniculata ameliorates hepatic steatosis, by improving glucose tolerance, and insulin sensitivity; reducing hyperinsulinemia, hyperglycemia & hyperlipidemia.[5] Further, it regulates inflammation mediated by the NF-κB pathway and ameliorates hepatic steatosis by suppressing FATP2-mediated fatty acid uptake in NAFLD to prevent hepatic damage.[6]

Boerhavia diffusa contains boeravinone B which alleviates gut dysbiosis and protects liver supporting its traditional use as a functional food for human health benefits.[7]

Picrorhiza kurroa reverses hepatic lipid accumulation by reducing fatty acid accumulation, oxidative stress, and mitochondrial dysfunction in HepG2 cells by modulating fatty acid uptake & synthesis. It reduces γ-Glutamyl Transpeptidase (GGT), Lactate Dehydrogenase (LDH), Alanine Amino-Transferase (ALT), Aspartate Amino-Transferase (AST) & Alkaline Phosphatase (ALP) levels; downregulates NF-kB, COX-2, IL-1β& IL-6.[8]

Therefore, it is observed that the ingredients of Livomyn modulate metabolic factors associated with NAFLD. In the current study, 8 weeks of treatment with Livomyn produced a significant reduction in all the parameters. All these results indicate that Livomyn is safe and effective in ameliorating NAFLD and its associated deranged metabolic parameters.

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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