International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2019): 7.583

Evaluation of Efficacy and Safety of NRL/2019/Nl in Liver Disorder Patients with Abnormal Liver Function Test: A Randomized, Parallel Arm, Interventional, Prospective Clinical Study

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Abstract: ***Aim:*** ***The present study is proposed to evaluate the efficacy and safety of NRL/2019/NL a nutraceutical product in patients with abnormal Liver Function Test (LFT).*** ***Settings and Design:*** ***This was a randomized, parallel arm, interventional, prospective clinical study with 100 subjects allocated intwo groups i.e. NRL/2019/NL (Test) or Marketed Product Group in 1:1 ratio.*** ***Methods and Material:*** ***Male and female subjects of age between 18 to 65 years of age with diagnosis of hepatic disorder with abnormal LFT were recruited and followed for 3 months with treatment. Laboratory testing, antioxidant enzyme levels and USG were performed on screening and day 90 of the study treatment. Change is these Laboratory parameters from baseline to 3 months were assessed.*** ***Results and conclusion:*** ***NRL/2019/NL is safe in management of liver disorder with abnormal liver function tests. NRL/2019/NL is significantly effective in normalizing elevated liver enzymes. NRL/2019/NL significantly improved antioxidant enzyme status like catalase and superoxide dismutase etc. It has resolved fatty liver and hepatomegaly evident in USG from baseline to day 90. NRL/2019/NL is significantly effective in improving symptoms of liver disorders such as abdominal pain, abdominal tenderness, nausea, vomiting, fatigue, jaundice and anorexia etc.***

Keywords: Liver disorder, fatty liver, herbal, clinical trial

1. Introduction

The liver functions are broadly classified under the following main categories: metabolic, vascular, secretory and excretory and immunological functions. Liver diseases, including hepatitis from B and C virus infections, alcoholic Liver disease (ALD), nonalcoholic fatty liver disease (NAFLD) and associated cirrhosis and hepatocellular carcinoma (HCC), are major causes of illness and mortality worldwide. There is even more propensity of getting liver disorders with sedentary lifestyle, wrong dietary choices. Many herbs and extracts are reported to produce hepatoprotective activities. Considering increasing prevalence of the liver injury, there is great need of supplementing liver with safer and natural ingredients which will contribute to the healing of existing damage caused to liver along with prevention of damage to liver. The Netsurf Communications Pvt. Ltd. has designed and developed the NRL/2019/NL capsules in liver management. The current research depicts the efficacy and safety of the NRL/2019/NL capsules in patients with deranged liver function test. [1].

2. Subjects and Methods

2.1 Selection criteria of subjects

Male and female subjects of age between 18 to 65 years of were randomized to either NRL/2019/NL (Test) group or Marketed Product Group (Standard group). Participants with Diagnosis of hepatic disorder with abnormal LFT with or without signs and symptoms such as dark-colored urine, light-colored stools, pruritus, pruritic red hives, fever, nausea, vomiting, anorexia, abdominal pain were included. Subjects with or without fatty liver changes observed in USGwere enrolled in the study. Subjects having serum total bilirubin level ≥ 2 mg/dl, or AST or ALT >2 times than normal values, and willing to sign inform consent form were enrolled.

Other causes of liver disease including evidence of chronic viral hepatitis (Hepatitis B or C) and biliary obstruction were excluded. Use of either prednisolone or PTX within 6 weeks of admission were not considered in the study. AST >500 U/L or ALT >300 U/L were excluded. Subjects with advanced liver disease (e.g. ascites, bleeding esophageal varices and hepatic encephalopathy, hepatic cancer) were excluded. Subjects with serious illness, e.g., uncontrolled diabetes, multisystem failure, HIV, cancer, severe renal insufficiency, serious cardiovascular disease pregnant or lactating women were not considered in the trial.Other conditions, which in the opinion of the investigators, makes the patient unsuitable for enrollment or could interfere with his/her participation were excluded.

2.2 Intervention details

NRL/2019/NL is nutraceutical product with 700 mg herbal extract blend in veggie capsule. The key ingredients of the product are extracts of Swertiachirayita, Silybummariamum, Cichoriumendivia and Phyllanthusamarus etc.As per computer generated randomization list, subject were either randomized to test or standard group in 1:1 ratio. Subjects were advised to take given supplement in a dose of 1 tablet/capsule BD after meals with lukewarm water for 90 days.

3. Procedure

Male and female subjects of age between 18 to 65 years of age (both inclusive) attending outpatient department of study site(s) were screened for eligibility criteria. On screening visit, a written informed consent was obtained from subjects for their participation in the study. Subject's demographic details were collected along with medical, surgical and treatment history. Subject's current medication if any was noted in the case record from (CRF). The subject was considered for further evaluation as per the inclusion and exclusion criteria.

During screening visit and the entire study duration subjects was advised to refrain from nutraceutical, herbal or Ayurvedic medication.

All the subjective questionnaire scores and symptom gradation were recorded in CRF from baseline to end of study including follow ups. Subjects were critically examined for adverse events from baseline to end of study. At screening and end of study, blood samples were collected for serum antioxidant enzymes, and other biochemical parameters like LFT, KFT, CBC etc. Subjects USG was performed on screening and end of study. After completion of 3 months of study treatment, all the subjects were asked to stop trial medications and take advice of investigator for further treatment.

4. Results

In the present study, 110 subjects were screened. 4 subjects were screened failure as per the decision of investigator as were presenting liver cirrhosis and not following inclusion and exclusion criteria. Out of 106 subjects, 06 lost to follow up in the study hence 100 subjects were considered evaluable cases at the end of the study 50 in each group. Out of 100 completed subjects, the mean age of test group subjects was 38.4 ± 6.28 years and the mean age of standard group subjects was 36.5 ± 8.12 years.

4.1 Changes in liver parameters test between groups

There was significant decrease in elevated levels of liver enzymes from baseline to day 90 in both the treatment groups. When compared between groups, there was so significant difference was observed (p>0.05). It can be concluded from the data that test product is equally effective in reducing elevated liver enzymes than that of marketed standard product.

Table 1: Changes in liver parameters test between groups

Liver Function Test	Test Group (Mean ±SD)		Std. Group (Mean ±SD)	
	Baseline	Day 90	Baseline	Day 90
Bilirubin Total	2.08 ± 1.17	0.80 ± 0.38 *	1.80 ± 0.95	0.76 ± 0.36*
Bilirubin Direct	0.72± 0.59	0.35 ± 0.38 *	0.66 ± 0.45	0.21 ± 0.09*
Bilirubin Indirect	1.37 ± 0.68	0.51 ± 0.21 *	1.15 ± 0.59	0.55 ± 0.28*
Aspartate Aminotransferase (SGOT)	86.87 ± 70.88	30.44 ±17.39 *	85.23 ±67.86	27.81 ±16.94*
Alkaline Transaminase (SGPT)	69.12 ±48.51	34.66 ±21.50 *	67.82 ±40.62	35.46 ±25.24*
Alkaline Phosphatase	136 ± 147.83	99.60 ±33.15 *	112.77 ±43.09	96.35 ± 21.29 *
Gamma GlutamylTrasferase (GGTP)	74.46 ± 101.69	42.18 ±58.48 *	70.34 ±121.05	34.41 ± 20.52 *
Total Proteins	7.37 ± 0.78	6.62 ± 2.10 *	7.32 ± 0.57	7.36 ± 0.56 ns
Serum Albumin	4.20 ±0.51	4.56 ± 1.14 ns	4.26 ± 0.54	4.18 ± 0.50 ns

ANOVA followed by Sidak's Multiple Comparison Test Within group analysis Non-significant (ns) = (>0.9999), Significant*(P=<0.0001),between group analysis Non-significant (NS) = (>0.9999)

4.2 Changes in Serum antioxidant enzyme status:

In test group and standard group there was significant (p<0.0001) improvement in the erythrocytic catalase and superoxide dismutase i.e. CAT and SOD levels from baseline to day 90 in respective groups. When compared between groups, the change in the enzyme levels were not statistically significant (p>0.05).

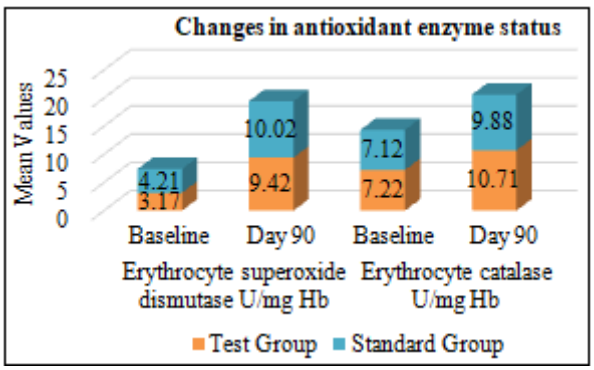

Figure 1: Changes in Serum antioxidant enzyme status in test groups:

4.3 Changes in severity of symptoms like anorexia, fatigue, abdominal pain, nausea etc.

4.3.1Abdominal pain

Table 2: Abdominal Pain

Test Group				
Duration in Days	Score 0 None	Score 1 Mild	Score 2 Moderate	Score 3 Severe
Baseline	2	14	33	1
Day 30	23*	2	1	0
Day 60	47*	3	0	0
Day 90	47*	3	0	0
Std. Group				
Baseline	12	36	2	0
Day 30	26*	24	0	0
Day 60	46*	4	0	0
Day 90	46*	4	0	0

Within group: Chi- Square Test, Significant*(P≤0.0001).

In both treatment groups i.e. test and standard groups, the number of subjects experiencing moderate to severe abdominal pain got shifted gradually to mild to no abdominal pain. The comparison of shifting number of subjects from moderate to no abdominal pain was statistically significant (P≤0.0001) within group from baseline to end of study i.e. day 90. The comparison between groups revealed non-significant change of shifting subjects from moderate to no abdominal pain grading.

4.3.2 Abdominal Tenderness

Table 3: Abdominal Tenderness

Test Group				
Duration in Days	Score 0 None	Score 1 Mild	Score 2 Moderate	Score 3 Severe
Baseline	11	28	9	2
Day 30	35*	15	0	0
Day 60	48*	2	0	0
Day 90	48*	2	0	0
Std. Group				
Baseline	11	25	14	0
Day 30	37*	17	0	0
Day 60	49*	1	0	0
Day 90	49*	1	0	0

Within group: Chi- Square Test, Significant*(P≤0.0001).

In both treatment groups i.e. test and standard groups, the number of subjects experiencing moderate to severe abdominal tenderness got shifted gradually to mild to no abdominal tenderness. The comparison of shifting number of subjects from moderate to no abdominal tenderness was statistically significant (P≤0.0001) within group from baseline to end of study i.e. day 90. The comparison between groups revealed non-significant change of shifting subjects from moderate to no abdominal tenderness grading.

4.3.3 Nausea

Table 4: Nausea

Test Group				
Duration in Days	Score 0 None	Score 1 Mild	Score 2 Moderate	Score 3 Severe
Baseline	11	28	9	2
Day 30	35*	15	0	0
Day 60	48*	2	0	0
Day 90	48*	2	0	0
Std. Group				
Baseline	11	25	14	0
Day 30	37*	17	0	0
Day 60	49*	1	0	0
Day 90	49*	1	0	0

Within group: Chi- Square Test, Significant*(P≤0.0001).

In both treatment groups i.e. test and standard groups, the number of subjects experiencing moderate to severe nausea got shifted gradually to mild to no nausea. The comparison of shifting number of subjects from moderate to no nausea was statistically significant (P≤0.0001) within group from baseline to end of study i.e. day 90. The comparison between groups revealed non-significant change of shifting subjects from moderate to no nausea grading.

4.3.4 Vomiting

Table 5: Vomiting

Test Group				
Duration in Days	Score 0 None	Score 1 Mild	Score 2 Moderate	Score 3 Severe
Baseline	17	29	4	0
Day 30	49*	1	0	0
Day 60	50*	0	0	0
Day 90	50*	0	0	0
Std. Group				
Baseline	21	27	2	1
Day 30	50*	0	0	0
Day 60	50*	0	0	0
Day 90	50*	0	0	0

Within group: Chi- Square Test, Significant*(P≤0.0001)

In both treatment groups i.e. test and standard groups, the number of subjects experiencing moderate to severe vomiting got shifted gradually to mild to no vomiting. The comparison of shifting number of subjects from moderate to no vomiting was statistically significant (P≤0.0001) within group from baseline to end of study i.e. day 90. The comparison between groups revealed non-significant change of shifting subjects from moderate to no vomiting grading.

4.3.5 Fatigue

Table 6: Fatigue

Test Group				
Duration in Days	Score 0 None	Score 1 Mild	Score 2 Moderate	Score 3 Severe
Baseline	1	17	29	3
Day 30	3*	41	6	0
Day 60	15*	35	0	0
Day 90	15*	35	0	0
Std. Group				
Baseline	2	9	29	10
Day 30	7*	37	6	0
Day 60	15*	35	0	0
Day 90	15*	35	0	0

Within group: Chi- Square Test,Significant*(P≤0.0001)

In both treatment groups i.e. test and standard groups, the number of subjects experiencing moderate to severe fatigue got shifted gradually to mild to no fatigue. The comparison of shifting number of subjects from moderate to no fatigue was statistically significant (P≤0.0001) within group from baseline to end of study i.e. day 90. The comparison between groups revealed non-significant change of shifting subjects from moderate to no fatigue grading.

4.3.6 Jaundice

Table 7: Jaundice

Test Group				
Duration in Days	Score 0 None	Score 1 Mild	Score 2 Moderate	Score 3 Severe
Baseline	14	23	12	1
Day 30	31*	19	0	0
Day 60	50*	0	0	0
Day 90	50*	0	0	0
Std. Group				
Baseline	16	19	14	1
Day 30	33*	16	1	0
Day 60	50*	0	0	0
Day 90	50*	0	0	0

Within group: Chi- Square Test, Significant*(P≤0.0001)

In both treatment groups i.e. test and standard groups, the number of subjects experiencing moderate to severe jaundice ie yellow discoloration of eyes got shifted gradually to mild to no yellow discoloration. The comparison of shifting number of subjects from moderate to no yellow discoloration was statistically significant (P≤0.0001) within group from baseline to end of study i.e. day 90. The comparison between groups revealed non-significant change of shifting subjects from moderate to no yellow discoloration grading.

4.3.7 Anorexia

Table 8: Anorexia

Test Group				
Duration in Days	Score 0 None	Score 1 Mild	Score 2 Moderate	Score 3 Severe
Baseline	18	17	14	1
Day 30	37*	11	2	0
Day 60	48*	2	0	0
Day 90	48*	2	0	0
Std. Group				
Baseline	21	9	17	2
Day 30	37*	12	1	0
Day 60	47*	3	0	0
Day 90	47*	3	0	0

Within group: Chi- Square Test, Significant*(P≤0.0001)

In both treatment groups i.e. test and standard groups, the number of subjects experiencing moderate to severe anorexia got shifted gradually to mild to no anorexia. The comparison of shifting number of subjects from moderate to no anorexia was statistically significant (P≤0.0001) within group from baseline to end of study i.e. day 90. The comparison between groups revealed non-significant change of shifting subjects from moderate to no anorexia grading.

4.4 Assessment score of Quality of Life through the General Health Questionnaire-28 (GHQ-28)

General Health Questionnaire-28 score was increased gradually from baseline to end of study reflecting improved quality of life in both the treatment groups. If compared between groups there was no significant difference observed. If compared within the groups, there was significant increase in the score from day 30.

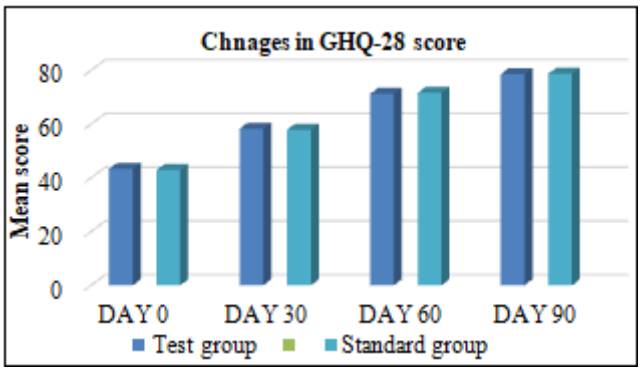

Figure 2: Changes in GHQ-28 Score

4.5 Changes in USG Abdomen

Table 9: Changes in USG Abdomen

Test Group (No. of subjects)		
USG abdomen inferences	Baseline	Day 90
No significant abnormality detected	24	40
Hepatomegaly with Grade I fatty liver	13	7
Grade II fatty liver	7	2
Hepatomegaly with grade II fatty liver	3	1
Hepatomegaly	3	0
Standard Group (No. of subjects)		
USG abdomen inferences	Baseline	Day 90
No significant abnormality detected	20	42
Hepatomegaly with Grade I fatty liver	15	4
Grade II fatty liver	5	3
Hepatomegaly with grade II fatty liver	5	1
Hepatomegaly	5	0

In test group at screening visit, 13 subjects were having hepatomegaly with grade I fatty liver and at the end of the study 7 subjects were having hepatomegaly with grade I fatty liver. 7 subjects were having grade II fatty liver at screening visit, after the treatment there were only 2 subjects with grade II fatty liver. At screening visit, 3 subjects reported to have hepatomegaly with grade II fatty liver and one subject reported to have hepatomegaly with grade II fatty liver at the end of the study. At screening visit, 3 subjects were having hepatomegaly, after treatment there were no subjects with hepatomegaly.

In standard group subjects with hepatomegaly and fatty liver shifted to normal USG. The difference of getting normal USG report of liver was non-significant. The details on pre and post treatment USG of study subjects is given in table 9.

4.6 Diagnosis of subjects

Table 10: Diagnosis of subjects

Findings from USG and Medical history	Test group (No. of subjects)	Std. group (No. of subjects)
Alcoholic Fatty Liver	23	22
Only ALD without Fatty Liver	20	22
Fatty Liver without Alcohol History	02	03
Infective Hepatitis	04	03
Drug Induced Hepatitis	01	01

As per the clinical judgment and medical history following table depicts the categorization of subjects based on the causative ailment for liver dysfunction.

4.7 Safety Assessment

Tolerability of study drugs assessed by physician and subjects: As per physician and subjects, both test and standard medicine were well tolerated for long term use.

4.8 Profile of adverse events

There were 18.9% subjects including both groups had adverse events during study period. Most common were body pain, cough, cold, throat irritation, vomiting, acidity and menstrual pain. Severity of events were mild among all. These adverse events were resolved completely after rescue medication. Study treatment was not stopped during these adverse events, hence were not related to study drug.

4.9 Laboratory parameters

All the safety laboratory parameters like complete blood count, KFT, blood sugar and urine routine were within normal range and there was no significant change after treatment as well in both the groups. This indicates safety of test and standard medication.

5. Discussion

Alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) are commonest chronic liver disease worldwide. NAFLD includes fatty liver (NAFL), steatohepatitis (NASH) and cirrhosis of liver. ALD ranges from steatosis, alcoholic hepatitis to cirrhosis and its complications [2].

Clinically, AFD as well as NAFLD are usually characterized by a mild to moderately deranged liver function test. There are limited options available as a therapeutic measures in conventional medicine for liver disorders like alcoholic cirrhosis, hepatitis or fatty liver. Many conventional medicine have well–documented side effects which presents need for any safe yet effective alternative in management of liver disorders.

In the present study, NRL/2019/NL is used as test medicine and is a polyherbal nutraceutical formulation as a blend of effective herbs mentioned in ancient literature of Ayurveda to be useful and effective in management of liver diseases. Treatment with polyherbal formula Liv 52 tablets by Himalaya Drug Company was used as standard control to compare and called as standard group. As the medicine used in the standard group is proven to be efficacious since many years in management of liver disorder, the aim of study was to check the effectiveness of test medication ie NRL/2019/NL against the standard to establish the clinical effectiveness. It can be concluded that NRL/2019/NL is equally safe and effective than Liv 52 tablets in the management of liver disorders.

The effectiveness of NRL/2019/NL can be explained based on the selection of ingredients and their individual and synergistic roles.

There are excellent herbs that are recommended in Ayurveda to help in the treatment of liver ailments are also used in NRL/2019/NL like- *Katuki (Picrorhizakurrooa), Kakamachi (SolanumNigrum), Punarnava (Boerrhaviadiffusa), Kiratatikta (Swertiachirata), Daruharidra (Berberisaristata)* etc.

*Kalmegh*present in test product has shown highly significant decrease in various elevated liver function tests in earlier studies[3].

Combination of *kalmegh* and *kutki*in test formulation herbs are useful as detoxifiers, helps to regenerate cells and prevents liver failure. It is useful in liver cirrhosis, jaundice, liver damage, due to alcohol toxins. *Punarnava*in test formulation is an excellent antioxidant help regenerate liver cells and can relieve liver enlargement and inflammation [4]. Studies have found that milk thistle may help reduce inflammation and liver damage in people with NAFLD. Some study shows that group of people taking milk thistle shows reduction in liver size [5].

*Milk thistle (Silymarin)*from the test product helps ease inflammation and promote cell repair. It has demonstrated relief from symptoms like jaundice, cirrhosis, liver cancer, and fatty liver disease. *Silymarin* acts as an antioxidant and modulates enzymes associated with the development of cellular damage, fibrosis and cirrhosis. These hepatoprotective effects were observed in patients with diabetes and alcoholic cirrhosis as a result of improved glycemic control [6].

*Kakamachi*present in test product extract can reduce raised biomarker for liver damage like SGPT, SGOT, GGT etc. It also can decrease proliferation of fibrous connective tissue in the liver. These protective effects likely stem from a reduction in oxidative stress due to antioxidant properties of the herbs, which turn modulates detoxification enzyme in the liver [7], [8].

*Ginseng*present in test product is proven to inhibit ROS production and the inflammation-signaling pathway. Moreover, as unique constituents of ginseng, ginsenosides have been found to inhibit liver carcinoma proliferation, promote liver regeneration, and prevent liver ischemia through anti-oxidative, anti-inflammatory, and anti-apoptotic mechanisms and thus can act as excellent hepatoprotective agent [9].

Curcuminfrom *Curcuma longa*is an excellent anti-inflammatory agent reported to influence multiple inflammatory and necrotic biomarkers like IL. TNF etc which can halt cirrhotic changes in liver [10].

Daruharidra present in test product is reported protect the liver cells against damage caused by free radicals as it has antioxidant, anti-inflammatory and hepatoprotective activities. *Daruharidra* might be beneficial in the management of non-alcoholic fatty liver disease (NAFLD). Berberine in *Daruharidra* helps to lower the level of triglycerides in the body. It also reduces the elevated levels of liver enzymes. It helps to reduce insulin resistance often associated with NAFLD [11].

L-ornithine present in test product is well researched compound helping in removal of accumulated urea as a result of compromised liver functionality in turn reducing oxidative damage and inflammation to liver [12].

It can be concluded from present study that NRL/2019/NL was significantly effective in normalizing liver functions in 90 days. At the end of the treatment with NRL/2019/NL, liver functions were within normal limits in all the subjects together with USG findings. NRL/2019/NL was significantly effective in improving symptoms of liver disorders such as abdominal pain, abdominal tenderness, nausea, vomiting, anorexia and fatigue from day 30 gradually to day 90.

In the present study, with the treatment of NRL/2019/NL the antioxidant enzyme levels like erythrocytic catalase and superoxide dismutase were improved.

Some of the herbs used in NRL/2019/NL are having excellent antioxidant and free radical scavenging activity thereby can be used for the prevention and treatment of liver damage. This antioxidant prevents and overrides liver injury from free radicals created by toxins improving the body's immune system, thus reducing the chance of viral and bacterial infections. Antioxidants prevent non-alcoholic fatty liver disease by abolishing risk factor such as oxidative stress and free radicals [13].

Anti-oxidant properties offered by NRL/2019/NL can reduce pain and inflammation in the body. It also improves the function of the liver which in turn helps in reducing the stress levels [14].

Abdomen ultrasound demonstrate "echogenic," liver which is denser than normal when expose to sound waves. Excess fat can lead to enlargement of liver.

In the NRL/2019/NL treated group at screening visit, 13 subjects were having hepatomegaly with grade I fatty liver and at the end of the study 7 subjects were having hepatomegaly with grade I fatty liver. 7 subjects were having grade II fatty liver at screening visit, after the treatment there were only 2 subjects with grade II fatty liver. At screening visit, 3 subjects reported to have hepatomegaly with grade II fatty liver and one subject reported to have hepatomegaly with grade II fatty liver at the end of the study. At screening visit, 3 subjects were having hepatomegaly, after treatment there were no subjects with hepatomegaly. There were 24 subjects showing no abnormality at baseline. At day 90, after treatment of NRL/2019/NL there were 40 subjects showing no abnormality in USG. It was evident from the present study that NRL/2019/NL led to improvement in USG readings.

The ingredients of study drug possess heaptoprotective activity against various heapatotoxins such as alcohol, drugs, viruses and chemicals. Ingredients beneficial in stabilization of elevated liver enzymes, increases bile secretion (Cholerectic property) from liver and also enhance overall liver function. By the virtue of synergistic activity of the ingredients, the study drug is effective in liver disorder patients with abnormal liver function tests.

Excellent drug tolerability of test and standard medication was reported by subjects and physician at the end of the study. No significant post treatment change in any of the lab investigations were observed. Also no significant post treatment change in vitals such as pulse rate, blood pressure, body temperature and respiratory rate were observed, suggesting study drug is safe in liver disorder patients with abnormal liver function tests. From the present study it can be concluded that NRL/2019/NL is safe and effective in improving liver function in subjects suffering from liver disorders.

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