IJPSR (2020), Volume 11, Issue 8 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 10 September 2019; received in revised form, 04 January 2020; accepted, 04 March 2020; published 01 August 2020

EVALUATION AND COMPARISON OF HEPATOPROTECTIVE ACTIVITY OF LIVSPLIN SYRUP AND LI- VERVE TONIC FORMULATIONS AGAINST CARBON TETRACHLORIDE INDUCED HEPATOTOXICITY IN RATS

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Keywords:

Alternative drugs, Synergistically, Beneficial, Hepatoprotective

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ABSTRACT: Liver diseases are a worldwide problem. Conventional drugs used in the treatment of liver diseases are sometimes inadequate and can have serious adverse effects like mild digestive problem, headache, nausea *etc*. It is necessary to search for alternative drugs and for treatment of liver disease to replace currently used drugs of doubtful efficacy and safety. Herbal therapies are free from side effects and toxicity, unlike allopathic medicines. Ayurvedic drugs are also acts by multiple pathways and shown full protection in liver disorders. Composition of marketed formulation Livsplin syrup (Test A) and Li- verve tonic (Test B) containing different plant extracts reported hepatoprotective and antioxidant activities. Thus these formulations may be synergistically or additively may show beneficial hepatoprotective activity with allopathic medicines. Hence, it may useful as alternative medicine to cure different kinds of liver diseases in man and animals. From our investigation, results were shown that administration of Li – verve tonic effectively protected against the loss of antioxidant activities of SOD, CAT, MDA respectively compared to control group and it is well known to serve diverse biological functions, protection of cells from oxidative damage by Reactive oxygen species & free radicals.

INTRODUCTION: The liver is the heaviest gland, weighing nearly about 1.4 kg in human body. It plays a vital role in regulating various physiological role and biotransformation of food, drugs, endogenous and exogenous substances [1]. These several biochemical reactions results in the generation of highly reactive free radicals. These free radicals attack the membrane lipids causing lipid peroxidation which alters the membrane permeability and causes tissue injury [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(8).4010-16

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(8).4010-16

Chronic liver diseases in general are increasingly wide spread and diseases of the liver in particular are considered a global public health problem. Chronic liver disease (CLD) substantially contributes mortality and morbidity rates. Worldwide, about 500 million individuals have CLD with a viral etiology. However, CLD also has non-viral etiology including alcoholic hepatitis, fatty liver, autoimmune hepatitis, and other unidentified causes [3].

Chronic hepatic diseases stand as one of the foremost health trouble worldwide, with liver cirrhosis and drug induced liver injury accounting ninth leading cause of death in western and developing countries. The common cause of acute liver diseases is drugs induced hepatotoxicity and accounts for 10% mortality [4].

Liver diseases are a worldwide problem. Conventional drugs used in the treatment of liver diseases are sometimes inadequate and can have serious adverse effects like mild digestive problem, headache, nausea *etc*. It is necessary to search for alternative drugs and for treatment of liver disease to replace currently used drugs of doubtful efficacy and safety [4].

Herbal- based therapeutics for liver disorders has been use in India for a long time and has been popularized world over by leading pharmaceuticals. The use of natural remedies for the treatment of liver diseases has a long history, starting with the Ayurvedic treatment, and other traditional medicines.

The 21st century has seen a paradigm shift towards the Therapeutic evaluation of herbal products in liver diseases models by carefully synergizing the strengths of the traditional systems of medicines with that of the modern concepts of evidence-based medicinal evaluation, standardization and randomization placebo controlled clinical trials to support clinical efficacy [5].

Many formulations containing herbal extracts are sold in the market for liver disorders. No significant scientific data available in modern therapeutics of few marketed Ayurvedic preparation for management of liver disorders by simple and precise effective herbal drugs [6].

Herbal therapies are free from side effects and toxicity, unlike allopathic medicines. Studies on hepatoprotective herbs will contribute to the benefit of the populations needing herbal treatment for hepatic disorders without involving the use of synthetic drugs and reducing the side effects of synthetic drugs. Ayurvedic drugs are also acts by multiple pathways and shown full protection in liver disorders.

Composition of marketed formulation Livsplin syrup (Test A) and Li-verve tonic (Test B) containing different plant extracts reported hepatoprotective and antioxidant activities. Thus these formulations may be synergistically or additively may show beneficial hepatoprotective activity with allopathic medicines. Hence, it may useful as alternative medicine to cure different kinds of liver diseases in man and animals.

The numbers of Ayurvedic formulations are available in the market. Among these formulation Livsplin syrup (Test A) and Li-verve tonic (Test B) has been recommended for hepatoprotective and also used as liver tonic but its pharmacological investigation is not done yet. Since, there was no scientific data available regarding hepatoprotective activity of these two Ayurvedic formulations.

Therefore, in the present investigation, carbon tetrachloride induced hepatotoxicity models was used to evaluate and compare the hepatoprotective activity of Ayurvedic formulations Livsplin syrup (Test A) and Li- verve tonic (Test B).

MATERIALS AND METHODS:

Animals: Male/female Albino rats (Wistar strain) weighing 150-200 gm, procured from animal house of Appasahe Birnale College of Pharmacy, Sangli, were used for the study. Animals were housed in well- ventilated room at 23 ± 2 ºC. With humidity of 65-70% and they were fed with a standard pellet diet with tap water. Procedures involving laboratory animals were in accordance with the guidelines of the Committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA).

List of materials used during experiments:

S. no.	Name of drug	Manufactured by
1	Silymarin	HISAR PHYTOEXTRACT Company Delhi.
2	Livsplin syrup (Test A)	Pat Pharmaceuticals Panvel, Maharashtra.
3	Li – verve tonic (Test B)	Cratus Life Care Andheri, India.

Experimental Design for Hepatoprotective Activity:

Carbon Tetrachloride Induced Hepatotoxicity: Rats were divided into five groups each groups containing 6 animals.

Group I: Served as Normal, Received distilled water 10 ml/kg p.o. for 7 days.

Group II: Served as control, Received Carbon tetrachloride in dose of 2 ml/kg i.p. (CCl_4 in paraffin 1:1 v/v) on 8th day.

Group III: Served as Standard, Received Silymarin 100 mg/kg orally daily for 7 days and

Carbon tetrachloride in dose of 2 ml/kg i.p. (CCl_4 in paraffin 1:1 v/v) on 8th day.

Group IV: Served as (Test A) Received Livsplin Syrup 2.59 ml/kg orally daily for 7 days and Carbon tetrachloride in dose of 2 ml/kg i.p. (CCl_4 in paraffin 1:1 v/v) on 8th day.

Group V: Served as (Test B) Received Li – verve tonic 2.71 ml/kg orally daily for 7 days and Carbon tetrachloride in dose of 2 ml/kg i.p. (CCl_4 in paraffin 1:1 v/v) on 8th day [6&7]

The drug solution was prepared and administered orally according to the body weight of the animals.

Assessment of Hepatoprotective Activity: In the present study the hepatoprotective activity was evaluated biochemically and histopathologically. After treatment, blood samples were removed from all animals by retro orbital puncture method. Serum was separated by centrifugation at 3000 rpm at 4 °C for 10 min and used for measurement of various biochemical markers like Alanine aminotransferase (ALT/SGPT), Aspartate aminotransferase (AST/ SGOT), Serum Alkaline Phosphatase (ALP) and Total bilirubin, Total protein, using commercially available kits. All the biochemical parameters were estimated. Finally, the animals were sacrificed after 24 h of administration on the 8th day and dissected the organ liver. Weight of each liver was taken and then histopathology of the liver samples was carried out. After dissection of livers of animals from all groups further determined antioxidant parameters like Superoxide dismutase (SOD), Catalase (CAT), Malondialdehyde (MDA) [6, 7, 8].

Statistical Analysis: The values were expressed as mean ± SEM. The statistical analysis was carried out by one way analysis of variance (ANOVA) followed by Dunnet's 't' - test. P values <0.05 were considered significance.

RESULTS:

Hepatoprotective Activity – in CCl_4 Induced Hepatotoxicity:

TABLE 1: EFFECT OF LIVSPLIN SYRUP (TEST A) AND Li - VERVE TONIC (TEST B) FORMULATIONS AGAINST CCl_4 INDUCED HEPATOTOXICITY

Groups	SGPT (U/L)	SGOT (U/L)	ALP (U/L)	TOTAL BILIRUBIN (mg/dl)	TOTAL PROTEIN (gm/dl)	LIVER WEIGHT (gm)
Normal (D/W) 10ml/kg	44.12 ± 0.6	74.21 ± 1.4	141.4 ± 0.7	0.6632 ± 0.6	6.257 ± 0.7	7.135 ± 0.4
Control (CCl_4) (2 ml/kg)	106.3#### ± 1.7	188#### ± 0.9	339.1#### ± 3.6	1.226#### ± 0.7	3.223#### ± 0.5	10.12 ± 0.4
Standard (Silymarin) (100mg/kg)	65.41**** ± 1.1	89.53**** ± 1.2	194**** ± 0.8	0.7447**** ± 0.9	5.54**** ± 0.6	7.605 ± 0.5
Test A (Livsplin syrup) (2.59 ml/kg)	76.65**** ± 1.1 (↓27.89)	164.1**** ± 1.5 (↓12.71)	283.1**** ± 0.7 (↓16.51)	0.7565**** ± 0.7 (↓38.52)	4.635**** ± 0.9 (↑30.46)	8.115 ± 0.8 (↓19.81)
Test B (Li – verve tonic) (2.71 ml/kg)	72.51**** ± 1.6 (↓31.78)	124.6**** ± 0.9 (↓33.72)	246.2**** ± 0.7 (↓27.39)	0.7635**** ± 0.8 (↓37.41)	5.348**** ± 0.5 (↑40.10)	7.635 ± 0.5 (↓24.55)

n = 6 animals in each group. Values are expressed as Mean ± SEM. Significance evaluated by one-way analysis of variance (ANOVA) followed by Dunnett's test control versus all. *****<0.05 is considered as criterion for significance. SGPT- Serum Glutamate Pyruvate Transaminase, SGOT- Serum Glutamate Oxaloacetate Transaminase, ALP- Alkaline Phosphatase. **####** Compared to normal (untreated). *****Level of significance p < 0.05; ********Level of significance p < 0.0001 compared to CCl_4 control. Values in bracket indicate % increase or decreae.

The serum levsels of SGPT, SGOT, ALP and T. bilirubin were significantly increased (p<0.0001) in Control while Livsplin syrup and Li – verve tonic rats treated with CCl_4 showed significant decrease in serum level (p<0.0001). Hepatic necrosis induced by CCl_4 (2ml/kg, i/p) intoxication elevated levels of serum biochemical parameters: SGPT, SGOT, ALP, T. bilirubin level and decrease the level of T. protein. The total liver weight was also increased significantly which was indicating acute hepatocellular damage and fatty degeneration.

The results shown by the Livsplin syrup (Test A) and Li – verve tonic (Test B) Formulations are statistically significant (p<0.0001). The effects of Livsplin syrup and Li - verve tonic (Test B)

Formulations on enzymes levels, T. bilirubin and liver weight shows that Livsplin syrup (Test A) and Li – verve tonic (Test B) formulations could offer significant degree of protection against CCl_4 induced hepatotoxicity

Antioxidant Activity- in CCl_4 Induced Hepatotoxicity:

TABLE 2: EFFECT OF LIVSPLIN SYRUP (TEST A) AND Li – VERVE TONIC (TEST B) FORMULATIONS ON VARIOUS ANTIOXIDANT ENZYMES AGAINST CCl_4 INDUCED HEPATOTOXICITY

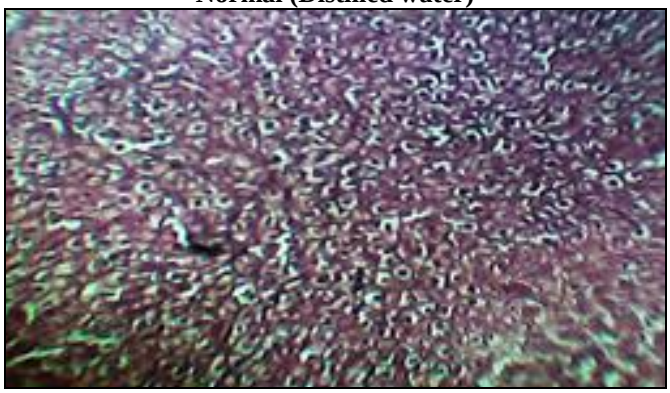
Groups	SOD (U/mg of protein)	CAT (U/mg of protein)	MDA (nmole/gm liver)
Normal (D/W) 10ml/kg	41.53 ± 0.3	34.69 ± 0.2	0.5885 ± 0.4
Control (CCl_4) (2 ml/kg)	9.17#### ± 0.2	5.816#### ± 0.3	12.67#### ± 0.4
Standard (Silymarin) (100mg/kg)	28.23**** ± 0.2	25.15**** ± 0.3	2.617**** ± 0.7
Test A (Livsplin syrup)	17.33**** ± 0.4	16.61**** ± 0.7	4.555**** ± 0.6
(2.59 ml/kg)	(↑88.98)	(↑185.59)	(↓64.08)
Test B (Li – verve tonic)	20.58**** ± 0.6	19.09**** ± 0.5	3.595**** ± 0.8
(2.71 ml/kg)	(↑124.42)	(↑228.23)	(↓71.62)

n = 6 animals in each group. Values are expressed as Mean ± SEM. Significance evaluated by one-way analysis of variance (ANOVA) followed by Dunnett's test control versus all. *<0.05 is considered as criterion for significance. SOD - Superoxide dismutase, CAT- Catalase, MDA- Malondialdehyde. *Level of significance $p < 0.05$; ****Level of significance $p < 0.0001$ compared to CCl4 control. #### Compared to normal (untreated). Values in bracket indicate % increase or decrease.

Hepatic SOD and CAT activities in the CCl_4 induced group were reduced compared to normal group, while MDA activity was increased. These antioxidant enzyme activities statistically significantly greater in the group treated with Livsplin syrup (Test A) and Li – verve tonic (Test B) formulations SOD, CAT while reduced level of MDA respectively compared to control group.

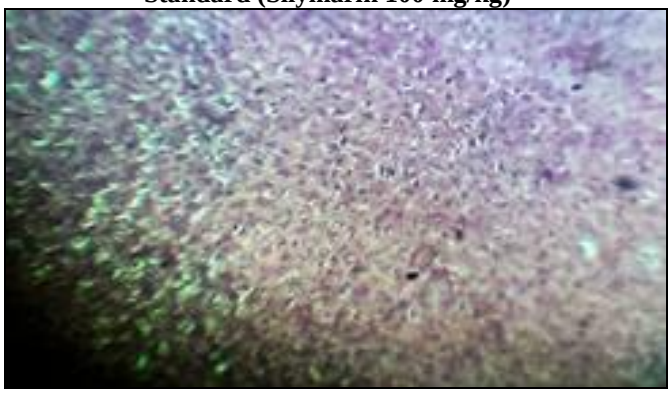
Histopathological Studies- In CCl_4 Induced Hepatotoxicity.

Normal (Distilled water)



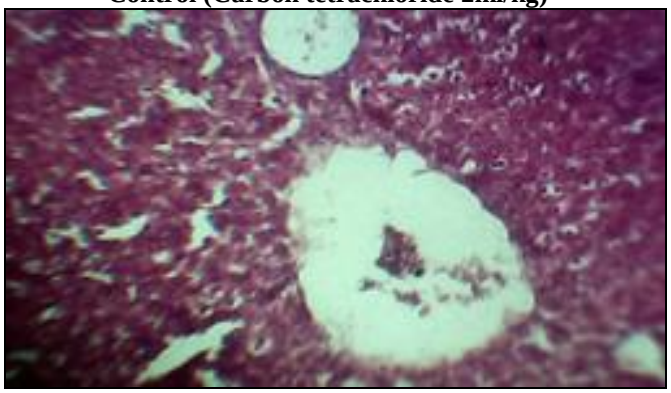
Liver section of normal showing hepatocytes

Standard (Silymarin 100 mg/kg)



Hydropic degeneration occurs (Reversible type of cell injury)

Control (Carbon tetrachloride 2ml/kg)



Infiltration by inflammatory cells and centrilobular necrosis

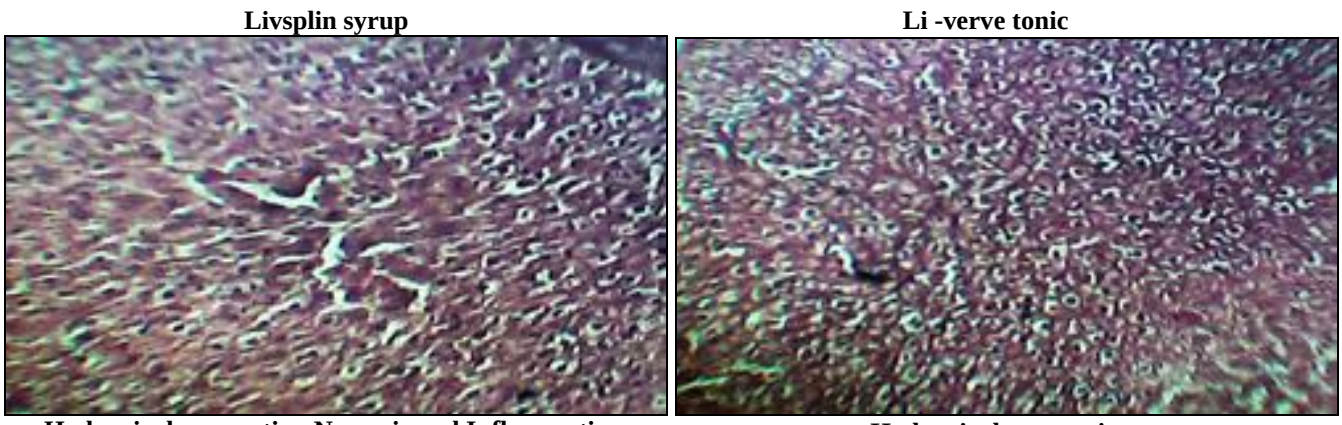


FIG. 1: REPRESENTATIVE PHOTOMICROGRAPHS OF HISTOPATHOLOGICAL CHANGES SHOWING EFFECT OF TEST MATERIALS ON THE RATS INTOXICATED WITH CARBON TETRACHLORIDE

DISCUSSION: Carbon tetrachloride is metabolized by cytochrome P-450 in endoplasmic reticulum and mitochondria with the formation of CCl_3O^-, a reactive oxidative free radical, which initiates lipid peroxidation. Administration of a single dose of CCl_4 to a rat produces, within 24 h, a centrilobular necrosis and fatty changes. The development of necrosis is associated with leakage of hepatic enzymes into serum [7].

CCl_4 not only initiate lipid peroxidation but also reduce CAT and SOD activities, and this depletion may result from oxidative modification of these proteins. CCl_4 is widely used to induce liver damage because it is metabolized in hepatocytes by cytochrome P450 [8, 9]. Increased levels of SGPT, SGOT and ALP in serum of the CCl_4 treated control animals indicates liver damage as these enzymes leak out from liver into blood at the instance of tissue damage, which is always associated with hepatonecrosis. Livsplin syrup (Test A) and Li – verve tonic (Test B) results showed percentage decrease in enzyme level of SGPT (↓27.89, ↓31.78) SGOT (↓12.71, ↓33.72) and ALP (↓16.51, ↓27.39) respectively, indicating protection against liver damage. ALP activity is related to functioning of the hepatocytes. Suppression of the increased ALP activity suggests the stability of biliary dysfunction in rat liver during chronic hepatic injury with CCl_4.

Diminution of total protein by CCl_4 is a further indication of liver damage. Livsplin syrup (Test A) and Li – verve tonic (Test B) has increased (↑30.46 & ↑40.1%) the levels of serum total protein towards respective normal value, which reveals hepatoprotective activity. Stimulation of protein synthesis has been advanced as a contributory hepatoprotective mechanism which accelerates the regeneration process and the production of liver cells [9]. Also, weight of liver was significantly increased in CCl_4 treated control group, but there was significant reduction observed in Livsplin syrup (Test A) and Li – verve tonic (Test B) treated groups (↓19.81 & ↓24.55) respectively. A significant reduction in liver weight supports this finding [9].

Our results showed that administration of Livsplin syrup (Test A) and Li - verve tonic (Test B) effectively protected against the loss of antioxidant activities of SOD (↑88.98, ↑124.42), CAT (↑185.59, ↑228.23), MDA (↓64.08, ↓71.62) respectively compared to control group and it is well known to serve diverse biological functions, including protection of cells from oxidative damage by Reactive Oxygen Species and free radicals.

In histopathological study, hepatocytes of normal group were shown a normal histological architecture in all models. It has been observed that CCl_4 causes inflammatory cells infiltration, fatty degeneration and centrilobular necrosis. These histopathological findings revels that hydropic degeneration occurs and significantly improved the structure of hepatic cells. The present study supports agreement with previous studies [9]. Treatment with Livsplin syrup (Test A) and Li-verve tonic (Test B) hydropic degeneration occurs, which is characteristic feature of reversible cell injury indicates significantly improved the structure of hepatic cells. The liver sections of rats treated

with Livsplin syrup (Test A) and Li-verve tonic (Test B) and Silymarin along with CCl_4 were shown a sign of protection.

Livsplin Syrup (Test A) Contains: *Boerhasavia diffusa* [10], *Zea mays* [11] *Eclipta alba, Tecomella undulata, Aegle marmelos* [12], *Emblica ribs, Zingiber officinale, Vitis vinifera, Terminalia chebula* [13], *Ipomoea turpethum* [14].

Li-verve tonic (Test B) Contains: *Phyllanthus niruri* [15], *Eclipta alba, Boerhaavia diffusa* [10], *Andrographis paniculata, Tephrosia purpurea* (Linn) [16], *Tinospora cordifolia* [17], *Amour rohituka, Picrorrhiza kurrooa, Zingiber officinale, Longum - pipers*

Li- verve tonic (Test B) containing *Phyllanthus niruri* plant extract. The presence of phenolic compounds, glycosides, flavonoids, flavonols, polyphenols, phenolic compounds, phenylpropanoids, protein, vit. E. is present in *Phyllanthus niruri* which are known antioxidants reported by Danladi S *et al*., (2018). The presence of all these compounds may contribute for high free radical scavenging activity. Phenolic compounds, by virtue of their hydrogen donating ability, forming aryloxyl radicals, act as free radical scavengers and quench the lipid peroxidation.

Further it has been already reported that phyto-chemical constituents like phenolic compounds, flavonoids are showed hepatoprotective activity in various experimental models and hence flavonoids and phenol containing herbal extracts are used in various hepatoprotective formulations [4, 18].

Li-verve tonic (Test B) showed most significant effect than Livsplin syrup (Test A). The following reasons that might be responsible for significant hepatoprotective effect of Li – verve tonic (Test B) compared to Livsplin syrup (Test A).

1. The dose of Li-verve tonic (Test B) (2.71 ml/kg) is more than the Livsplin syrup (Test A) (2.59 ml/kg).

2. The Li-verve tonic (Test B) contains 10 number of plant extracts in its composition as compared to Livsplin syrup (Test A) contains 9 number of plant extracts. Among that 8 plants from Li-verve tonic formulation showed antioxidant property than Livsplin syrup which contain 5 antioxidant herbal plants which showed antioxidant properties.

Li-verve tonic (Test B) contains herbal antioxidant plants namely, *Phyllanthus niruri* [15], *Eclipta alba, Boerhaavia diffusa* [10], *Tephrosia purpurea* (Linn) [16], *Tinospora cordifolia* [17], *Amour rohituka, Picro-rrhiza kurrooa, Zingiber officinale*; that might be responsible for significant hepatoprotective activity which was also confirmed by result of biochemical and histopathological parameters of the Livsplin syrup (Test A) and Li-verve tonic (Test B) formulations.

Thus result concluded that Li-verve tonic (Test B) is most significant hepatoprotective formulation compared to Livsplin syrup (Test A).

CONCLUSION: The present study revealed the following conclusions:

- Livsplin syrup and Li – verve tonic demonstrated a significant Hepatoprotective activity against Carbontetrachloride induced hepatotoxicity in rats.
- Moreover, Li – verve tonic has shown significant Hepatoprotective activity in comparison to Livsplin syrup which is also confirmed by result of biochemical parameters and histopathological findings.

ACKNOWLEDGEMENT: Authors are thankful to Dr. Padma Ladda, Associate Professor, Department of Pharmacology, ABCP, Sangli, Maharashtra, India, Dr. Nilofar Naikwade, Professor and Head, Department of Pharmacology, ABCP, Sangli, Maharashtra, India, Tabassum Shikalgar, Assistant Professor, Department of Pharmacology, ABCP, Sangli, Maharashtra, India, and Shirish Patil, Assistant Professor, Department of Pharmacology, ABCP, Sangli for their valuable support.

CONFLICTS OF INTEREST: Nil

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How to cite this article:
Kagadi NM, Ladda PL and Naikwade NS: Evaluation and comparison of hepatoprotective activity of livsplin syrup and li- verve tonic formulations against carbon tetrachloride induced hepatotoxicity in rats. Int J Pharm Sci & Res 2020; 11(8): 4010-16. doi: 10.13040/IJPSR.0975-8232.11(8).4010-16.