



## Viral Hepatitis – A Review Article

P. Hamsarekha<sup>1\*</sup>, B. Anuhya<sup>1</sup>, K. Bandhavi<sup>1</sup>, M. Snehanjali<sup>1</sup>, Ravi Chander Thatipelli<sup>1,2</sup>, Sandeep Goud Mitta<sup>1</sup>

<sup>1</sup>Department of Pharmacy Practice, Vaagdevi Pharmacy College, Warangal

<sup>2</sup> Faculty of Pharmaceutical Sciences, UCSI University, Cheras, Kuala Lumpur, Malaysia

**\*Corresponding Author:**

**Dr. P. Hamsarekha Pharm. D**

Assistant Professor, Department of Pharmacy Practice, Vaagdevi Pharmacy College  
Bollikunta, Warangal, Telangana, India- 506005

Type of Publication: Review Paper

Conflicts of Interest: Nil

### Abstract

Hepatitis is inflammation of the liver that can result from a variety of causes such as alcohol overconsumption, autoimmune, medications, or toxins. Hepatitis can be further classified into acute and chronic. If inflammation of the liver lasting for less than 6 months, is termed as acute hepatitis and greater than 6 months is termed as chronic hepatitis. Hepatitis is a significant public health issue in developing countries, having varying morbidity and mortality rates. Hepatitis A and E infections are typically self – limiting and do not result in chronic liver disease, but can cause significant morbidity and mortality in people with underlying liver disease. Hepatitis B is a major global health issue, about 257 million people are living with chronic hepatitis B infection. Hepatitis D is relatively rare and usually infect people who are already infected with hepatitis B. Clinical pharmacist can play a major role in reducing the spread of infection by properly educating the patient about spread of disease and hygiene.

**Keywords:** Hepatitis, Liver, Morbidity, Mortality, Clinical Pharmacist

### Introduction

Viral hepatitis has been a redoubtable challenge, with proved outbreaks 5000 years ago in China and analogous jaundice descriptions by Hippocrates in the 5th century BC in the Island of Thassos<sup>[1]</sup>. Hepatitis is inflammation of the liver that can result from a variety of causes such as alcohol overconsumption, autoimmune, medications, or toxins. Viral infection is the most frequent cause of hepatitis. Hepatitis A, B and C are most common types of hepatitis whereas hepatitis D and hepatitis E are less commonly encountered<sup>[2]</sup>. Hepatitis B and D are the most chronic types of Hepatitis and leads to Liver cirrhosis and Liver Cancer, and are responsible for a significant number of deaths each year. The severity of hepatitis can range from mild and self-limiting to severe illness requiring liver transplantation based on causative factor. Based on

the duration of the inflammation, Hepatitis can be further classified into acute and chronic<sup>[3]</sup>. If inflammation of the liver lasting for less than 6 months, is termed as acute hepatitis and greater than 6 months is termed as chronic hepatitis. Acute hepatitis is usually self-resolving but it can cause fulminant liver failure based on the etiology. Whereas, chronic hepatitis can cause liver damage that includes hepatocellular carcinoma, liver fibrosis, cirrhosis, and features of portal hypertension leading to significant morbidity and mortality<sup>[4]</sup>.

### Epidemiology

Millions of people Worldwide are getting affected by Hepatitis and it is a global health issue. Hepatitis is a significant public health issue in developing countries, having varying morbidity and mortality

rates. 1.4 million people die every year from viral hepatitis related cirrhosis and Liver cancer<sup>[5]</sup>. Hepatitis A and E infections are typically self – limiting and do not result in chronic liver disease, but can cause significant morbidity and mortality in people with underlying liver disease.

### Hepatitis A

Hepatitis A is RNA virus belonging to *Picornaviridae* family. Hepatitis A is common in countries with poor sanitation and hygiene practices. In developed countries, with better sanitation and wide spread vaccination programmes Hepatitis A is less common<sup>[6]</sup>.

### Etiology

Hepatitis A is caused by the Hepatitis A virus (HAV) and is usually transmitted through contaminated food or water. People who travel to areas with poor sanitation are at higher risk of contracting hepatitis A. Incubation period of Hepatitis A ranges from 2 to 4 weeks rather it can be upto 8 weeks<sup>[7]</sup>.

### Clinical features

Acute hepatitis A ranges from mild incidence without any signs to severe cases with acute liver failure and death. It is usually a short-term illness, and the symptoms can include, vomiting, abdominal pain, fatigue, nausea, and jaundice and typically spreads through contaminated food and water<sup>[8]</sup>. The incubation period of hepatitis A virus is four weeks. Acute infections are more severe with higher mortality in adults than children. Symptoms are usually anorexia, malaise, vomiting, nausea and jaundice. Relapses are not common, and the infection does not develop into chronic hepatitis. Only less than 1% of cases result in fulminant hepatic failure. Within 6-month period of the initial infection 10%-15% of patients present with relapsing course<sup>[9]</sup>. Serum aminotransferases above 1000 U/dL are noted, alkaline phosphatase below 400 U/L and total bilirubin typically  $\leq 10$  mg/dL. Usually serum alanine aminotransferase (ALT) is greater than aspartate aminotransferase (AST)<sup>[10]</sup>.

### Hepatitis B

Hepatitis B is a major global health issue, about 257 million people are living with chronic hepatitis B infection<sup>[11]</sup>.

### Etiology

HBV is a double-stranded DNA virus and belongs to the *Hepadnaviridae* family<sup>[12]</sup>. It is typically caused by the Hepatitis B virus (HBV), and spreads through contact with infected blood or body fluids. Other causes include unprotected sex, sharing needles or other drug paraphernalia, and perinatal transfer. This virus can cause both acute and chronic infections and leads to severe liver damage if untreated. The incubation period of HBV is 90 days or, ranges from 60 to 150 days. Perinatal transmission often occurs at birth or in neonatal period, and the intended result of neonatal vaccination in utero, infection is uncommon. The primary determinants of vertical transmissions are detected HBeAg status and hepatitis B virus DNA levels and the transmission rate in HBeAg-positive women is 90% without vaccination in differentiation with 32% for HBeAg-negative women<sup>[13]</sup>.

### Clinical features

Acute HBV infection can range from a subclinical disease to an icteric phase, the later being the less common presentation<sup>[14]</sup>. Patients may present fatigue, nausea, vomiting and right upper quadrant pain before or during icteric onset. less than 1% of cases may present fulminant hepatitis. During acute phase, there is a rapid HBV viral load increase in the 10000-100000 ng/mL range, along with ALT and AST elevation in the 1000-2000 IU/L range, and total bilirubin elevation<sup>[15]</sup>. At this point, HBsAg and IgM core antibody (HBcAb) become positive, supporting an acute HBV diagnosis. Although a subset of acute HBV can have resolution of the infection with liver enzyme normalization, if the ALT remains elevated after 6 months from initial presentation, a chronic HBV phase is established.

Chronic HBV may develop in patients exposed at a younger age, with genetic predisposition or in those that did not develop symptoms when acute HBV infection occurred<sup>[16]</sup>. These patients are usually asymptomatic for years, unless there is HBV exacerbation or development of complications<sup>[17]</sup>. The occurrence of HBV exacerbations is explained by four phases which reflects disease activity. The first phase which is known as immune tolerant phase showing marked elevation of HBV titers and positive HBeAg, without ALT elevation or liver inflammation at this time patients are asymptomatic. The second phase i.e., immune clearance phase is characterized by activation of the immune system, leading to elevation

of ALT at least five-fold the upper limit, HBV DNA decrease and there is histological evidence of inflammation, possibly leading to fatigue, jaundice, and right upper quadrant pain. The third phase which is immune control phase shows negative HBeAg, as there is seroconversion to positive HBeAb (hepatitis B e antibody) and undetectable to low HBV DNA titers. The fourth phase which is immune active phase is characterized by elevated ALT and HBV DNA because of triggers such as hepatitis D virus (HDV) superinfection or immunosuppression, leading to symptoms as seen in the second phase with potential risk for acute liver failure. The disease can fluctuate between the third and fourth phases<sup>[18]</sup>.

### Hepatitis C

Hepatitis C is also a major global health issue, with an estimated 71 million people living with chronic hepatitis C infection. According to WHO 71 million of population are living with hepatitis C infection in 2015 and measures about 1% of the world population. The distribution of each hepatitis C virus genotype differs in various geographical areas globally<sup>[19]</sup>.

### Etiology

Hepatitis C is enveloped, positive single-stranded small RNA virus that was first discovered as a member of the *Flaviridae* family and is the only member of genus *Hepacivirus*. It enters the body percutaneously through contaminated blood. It may also enter through organ transplantation, blood transfusions, sexual intercourse, perinatal transmission, hemodialysis, religious scarification, body piercings, tattoos, and immunoglobulin injection<sup>[20]</sup>. The incubation period of hepatitis C is 7 weeks and can range from 4 to 20 weeks. If left untreated virus can cause both acute and chronic infections and can even lead to serious liver damage<sup>[21]</sup>.

### Clinical features

HCV infection are mostly asymptomatic or can have nonspecific symptoms including fatigue, sleep disturbances, nausea, diarrhea, abdominal pain, anorexia, myalgia, arthralgia, weakness, depression, anxiety, and weight loss<sup>[22]</sup>. Patients who develop cirrhosis can eventually develop jaundice, ascites, and other stigmata of cirrhosis.

Serum aminotransferase levels are relatively stable in patients with chronic HCV infection. 1/3<sup>rd</sup> of patients have normal ALT; only one in four have a serum ALT more than twice the upper limit of normal range; others have slight increase in enzyme levels. Rarely, ALT may elevate more than ten times the upper limit<sup>[1]</sup>.

### Hepatitis D

Hepatitis D is less common than other types, and is typically found in people having Hepatitis B. Approximately 18 Million people are infected with Hepatitis D virus globally<sup>[23]</sup>.

### Etiology

Hepatitis D is caused by Hepatitis D virus (HDV). The hepatitis D is relatively rare and usually infect people who are already infected with hepatitis B. The incubation period of hepatitis D virus is approximately 2 to 8 weeks. Hepatitis D is spread through contact with infected blood or body fluids. The viral infection can lead serious liver damage if left untreated. Hepatitis D is the severe form of viral hepatitis which rapidly leads to cirrhosis of liver and increases risk of hepatocellular carcinoma and mortality rate when compared with hepatitis B<sup>[24]</sup>.

### Clinical features

The symptoms can be similar to those of Hepatitis B, but can also include more severe liver damage. Although tending to be severe clinical symptoms of Hepatitis D cannot be differentiated from other types of Hepatitis. It is the least common disease but more severe and show rapidly progressive form of viral hepatitis of all age groups<sup>[25]</sup>.

### Hepatitis E

Hepatitis E is more common in developing countries with poor sanitation and hygiene practices. The greatest incidence rate among cases are easily observable between 15 and 40 years of age groups<sup>[26]</sup>.

### Etiology

Hepatitis E is caused by Hepatitis E virus (HEV), which is typically spread through faecal-oral route and contaminated food and water<sup>[27]</sup>. The incubation period of hepatitis E virus is 2 to 9 weeks (average of 6 weeks). Hepatitis E is more common in developing countries with poor sanitation and hygiene practices and most common in developed

countries and it is usually known as short term illness. Hepatitis E is severe in pregnant women. Outbreaks of hepatitis E have been reported in areas affected by natural disasters or other emergencies.

**Clinical features**

This type of hepatitis is more common in developing countries, and is usually a short-term illness. Acute HEV infection is relatively asymptomatic or mildly symptomatic and can include malaise, fever, body aches, fatigue, nausea, vomiting, abdominal pain, and jaundice<sup>[28]</sup>

**Table 1 :** Characteristics of Hepatitis Viruses types

FEATURES	HEPATITIS A VIRUS (HAV)	HEPATITIS B VIRUS (HBV)	HEPATITIS C VIRUS (HCV)	HEPATITIS D VIRUS (HDV)	HEPATITIS E VIRUS (HEV)
Nucleic acid	RNA	DNA	RNA	Incomplete RNA	RNA
Serologic diagnosis	Ig M anti – HA	HBsAg	Anti – HCV	Anti - HDV	Anti - HEV
Mode of transmission	Fecal oral route	Blood	Blood	Needle	Water
Incubation period	15 - 45 days	40 - 180 days	20 - 120 days	30 - 180 days	14 - 60days
Epidemics	Yes	No	No	No	Yes
Chronicity	No	Yes	Yes	Yes	No
Liver cancer	No	Yes	Yes	Yes	No

Incomplete RNA : Requires presence of hepatitis B virus for replication.

**SEROLOGICAL TESTS**

**Table 2 :** Simplified diagnostic approach in patients presenting with Acute hepatitis

HBsAg	IgM Anti - HAV	IgM Anti - HBc	Anti - HCV	DIAGNOSTIC INTERPRETATION
+	-	+	-	Acute hepatitis B
+	-	-	-	Chronic hepatitis B
+	+	-	-	Acute hepatitis A super imposed on chronic hepatitis B
+	+	+	-	Acute hepatitis A and B
-	+	-	-	Acute hepatitis A
-	+	+	-	Acute hepatitis A and B ( HBsAG below detection threshold )
-	-	+	-	Acute hepatitis B ( HBsAG below detection threshold )
-	-	-	+	Acute hepatitis C

HBsAg , IgM Anti - HAV , IgM Anti – HBc , Anti – HCV comes under serological tests for patient’s serum.

**Table 3** : Clinical And Laboratory Features Of Chronic Hepatitis

TYPE OF HEPATITIS	DIAGNOSTIC TEST(S)	AUTO ANTI BODIES
Chronic hepatitis B	HBsAg, IgG anti – HBc, HBeAg, HBV DNA	Uncommon
Chronic hepatitis C	Anti – HCV, HCV RNA	Anti - LKM1
Chronic hepatitis D	Anti – HDV, HDV RNA, HBsAg, IgG anti - HBc	Anti - LKM3

**Treatment :****Non-Pharmacological Treatment**

Vaccination is necessary as per schedule. Avoid sexual activities with multiple partners and infected persons as the infection may spread through sexual activity easily. Avoid contaminated food and water. People who travel often should maintain proper hygiene and must immunize as per the schedule. Maintain proper dietary and nutritional supplements which are rich in Carbohydrates like rice, millets etc. Avoid in take of fat rich foods like red meat, milk products like butter, cheese, cream<sup>[31]</sup>. Avoid alcohol consumption and smoking as they will worsen the infection.

**Hepatitis A**

Treatment consists of supportive care as no specific drugs are available for HAV infection ; Prevention of HAV infection includes vaccination, immune globulin, and attention to hygienic practices.

**Hepatitis B**

Entecavir, tenofovir disoproxil fumarate, tenofovir alafenamide fumarate, and pegylated interferon alpha are currently the first-line anti-HBV agents recommended for chronic hepatitis B treatment; Prevention of HBV infection is focused on vaccination<sup>[32]</sup>. In hepatitis B condition we can manage with HBV vaccine. But in case of chronic condition, it is transmitted to foetus and causes the down's syndrome in pregnant women so it is necessary to immunize the new born with proper vaccine doses. Anti biotics like Ofloxacin (Dose : 200mg to 400mg tablet), cephalosporins and penicillin's of appropriate doses is prescribed.

Hepatoprotectives, Anti-viral agents like Lamivudine (Dose : 100 mg ; 150 mg; 300 mg tablet form and 5 mg/ mL ; 10 mg /mL oral solution) , Tenofovir ( Dose : 25 mg tablet), Entecavir (Dose : 0.5 mg to 1.0 mg ). The duration of therapy with anti-viral agents are of 9 months. In chronic conditions the therapy of the infection includes Interferon – alpha<sup>[33]</sup>.

**Hepatitis C**

Multiple combinations of direct-acting antivirals with high pangenotypic efficacy are used which results in high sustained virological response rates, excellent safety, and good tolerance, and is even useful for patients with advanced fibrosis and cirrhosis.

Therapy of hepatitis C includes Interferon – alpha and anti-viral agent like Ribavirin (Dose : 200 mg to 600 mg in tablet form; 6g/ vial inhalation solution ; 40mg/mL oral solution). Supportive care is given according to the symptoms and condition of the patient illness<sup>[33]</sup>.

**Hepatitis D**

There are no satisfactory drugs for HDV; Pegylated interferon alpha recommended for the treatment of chronic HDV infection, although limited by poor tolerance is usually avoided in patients with cirrhosis, active autoimmune disease, or certain psychiatric disorders.

**Hepatitis E**

There is no recommended treatment for acute HEV infections because it is usually self-limiting with spontaneous HEV clearance. Ribavirin is suggested to be an effective treatment for immunocompetent patients with severe hepatitis E; New anti-HEV drugs



are under investigation; T cell therapy may be an alternative to conventional medicines<sup>[32]</sup>

## CONCLUSION

Hepatitis can be a major health hazard if ignored or untreated. It can be avoided by following precautions and vaccinations. The recognition of epidemiological and clinical features of Hepatitis A, B, C, D and E is crucial to guide the diagnosis of these conditions. The medical advances which are evolved have allowed effectively diagnosing them and comprehensively establishing its multi-systemic impact in the population. Clinical Pharmacist plays a crucial role in educating patients regarding the disease spread and prevention.

**Conflict of Interest:** The author declares no conflict of interest.

**Consent for publication:** All the authors have read and approved the final version of the manuscript submitted.

**Acknowledgement:** The authors are thankful to Vaagdevi Pharmacy College, Bollikunta Warangal for their constant support.

## Abbreviations<sup>[29,30]</sup>:

HBsAg	: Hepatitis B surface antigen.
Anti - HCV	: Anti body to hepatitis C virus.
Anti - HDV	: Anti body to hepatitis D virus.
Anti - HEV	: Anti body to hepatitis E virus
IgM anti HAV	: Immunoglobulin M anti – hepatitis A virus,
IgM anti HBc	: Immunoglobulin M anti hepatitis B core,
HBc	: Hepatitis B core,
HBeAg	: Hepatitis B e antigen,
HBV	: Hepatitis B virus,
HCV	: Hepatitis C virus,
Anti HCV	: Anti Hepatitis C virus
HDV	: Hepatitis D virus
IgG	: Immunoglobulin G
LKM	: Liver Kidney Microsome <sup>[30]</sup> .

## References

1. Castaneda D, Gonzalez AJ, Alomari M, Tandon K, Zervos XB. From hepatitis A to E: A critical review of viral hepatitis. *World J Gastroenterol.* 2021 Apr 28;27(16):1691-1715. doi: 10.3748/wjg.v27.i16.1691. PMID: 33967551; PMCID: PMC8072198.
2. Zuckerman AJ. Hepatitis Viruses. In: Baron S, editor. *Medical Microbiology*. 4th ed. University of Texas Medical Branch at Galveston; Galveston (TX): 1996.
3. Dakhil N, Junaidi O, Befeler AS. Chronic viral hepatitis. *Mo Med.* 2009 Sep-Oct;106(5):361-5.
4. Ryder SD, Beckingham IJ. ABC of diseases of liver, pancreas, and biliary system: Acute hepatitis. *BMJ.* 2001 Jan 20;322(7279):151-3.
5. Jefferies M, Rauff B, Rashid H, Lam T, Rafiq S. Update on global epidemiology of viral hepatitis and preventive strategies. *World J Clin Cases.* 2018 Nov 6;6(13):589-599. doi: 10.12998/wjcc.v6.i13.589. PMID: 30430114; PMCID: PMC6232563.
6. T. Ravi Chander.; D. Pragnasree.; E. Sushma.; a prospective observational study on causes, consequences, risk factors, & treatment patterns in preterm birth. *World Journal of Pharmacy and Pharmaceutical Sciences*, 12(07), 2023, 1487-1496.
7. Lanini, Simone, Andrew Ustianowski, Raffaella Pisapia, Alimuddin Zumla, and Giuseppe Ippolito. "Viral hepatitis: etiology, epidemiology, transmission, diagnostics, treatment, and prevention." *Infectious Disease Clinics* 33, no. 4 (2019): 1045-1062.
8. Gholizadeh, Omid, Sama Akbarzadeh, Mohamad Ghazanfari Hashemi, Marjan Gholami, Parya Amini, Zahra Yekanipour, Raheleh Tabatabaie, Saman Yasamineh, Parastoo Hosseini, and Vahdat Poortahmasebi. "Hepatitis A: viral structure, classification, life cycle, clinical symptoms, diagnosis error, and vaccination." *Canadian Journal of Infectious Diseases and Medical Microbiology* 2023 (2023).
9. Matheny SC, Kingery JE. Hepatitis A. *Am Fam Physician.* 2012 Dec 01;86(11):1027-34; quiz 1010-2.

1. Koff RS. Clinical manifestations and diagnosis of hepatitis A virus infection. *Vaccine*. 1992;10 Suppl 1:S15–S17.
10. MacLachlan, Jennifer H., and Benjamin C. Cowie. "Hepatitis B virus epidemiology." *Cold Spring Harbor perspectives in medicine* 5, no. 5 (2015): a021410.
11. Scaglioni PP, Melegari M, Wands JR. Recent advances in the molecular biology of hepatitis B virus. *Baillieres Clin Gastroenterol*. 1996;10:207–225.
12. Burns, Gregory S., and Alexander J. Thompson. "Viral hepatitis B: clinical and epidemiological characteristics." *Cold Spring Harbor perspectives in medicine* (2014): a024935.
13. Liaw YF, Tsai SL, Sheen IS, Chao M, Yeh CT, Hsieh SY, Chu CM. Clinical and virological course of chronic hepatitis B virus infection with hepatitis C and D virus markers. *Am J Gastroenterol*. 1998;93:354–359
14. Jindal A, Kumar M, Sarin SK. Management of acute hepatitis B and reactivation of hepatitis B. *Liver Int*. 2013;33 Suppl 1:164–175.
15. Yan ZH, Fan Y, Wang XH, Mao Q, Deng GH, Wang YM. Relationship between HLA-DR gene polymorphisms and outcomes of hepatitis B viral infections: a meta-analysis. *World J Gastroenterol*. 2012;18:3119–3128.
16. Lapointe-Shaw L, Chung H, Holder L, Kwong JC, Sander B, Austin PC, Janssen HLA, Feld JJ. Diagnosis of Chronic Hepatitis B Peri-Complication: Risk factors and Trends over Time. *Hepatology*. 2020.
17. Croagh CM, Lubel JS. Natural history of chronic hepatitis B: phases in a complex relationship. *World J Gastroenterol*. 2014;20:10395–10404.
18. Coppola, Nicola, Loredana Alessio, Lorenzo Onorato, Caterina Sagnelli, Margherita Macera, Evangelista Sagnelli, and Mariantonietta Pisaturo. "Epidemiology and management of hepatitis C virus infections in immigrant populations." *Infectious Diseases of Poverty* 8, no. 02 (2019): 13-22.
19. Murphy EL, Bryzman SM, Glynn SA, Ameti DI, Thomson RA, Williams AE, Nass CC, Ownby HE, Schreiber GB, Kong F, Neal KR, Nemo GJ. Risk factors for hepatitis C virus infection in United States blood donors. *Hepatology*. 2000;31:756–762.
20. Meringer H, Shibolet O, Deutsch L. Hepatocellular carcinoma in the post-hepatitis C virus era: Should we change the paradigm? *World J Gastroenterol*. 2019 Aug 7;25(29):3929-3940. doi: 10.3748/wjg.v25.i29.3929. PMID: 31413528; PMCID: PMC6689810.
21. Evon DM, Stewart PW, Amador J, et al. antiviral therapy for chronic hepatitis C: Results from a large US multi-center observational study. *PLoS One*. 2018; 13:e0196908.
22. Mehta P, Reddivari AKR. Hepatitis. [Updated 2022 Oct 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023.
23. Romanivna, Melenko Svitlana, Skrypnyk Valentyna Valentynivna, and Glukhova Anna Yosifivna. "VIRAL HEPATITIS D: ETIOLOGY, EPIDEMIOLOGY, PATHOGENESIS, CLINIC, TREATMENT, DIAGNOSIS AND PREVENTION." In *Colloquium-journal*, no. 9 (168), pp. 64-68. 2023.
24. Farci, Patrizia, and Grazia Anna Niro. "Clinical features of hepatitis D." In *Seminars in liver disease*, vol. 32, no. 03, pp. 228-236. Thieme Medical Publishers, 2012.
25. Krawczynski, Krzysztof M.D., Ph.D.\*, 1. Hepatitis E. *Hepatology* 17(5):p 932-941, May 1993. | DOI: 10.1002/hep.1840170525
26. Xiong XY, Liu X, Yin X. [Research progress in the etiology of hepatitis type E virus]. *Zhonghua Gan Zang Bing Za Zhi*. 2023 May 20;31(5):460-465. Chinese. doi: 10.3760/cma.j.cn501113-20230221-00072. PMID: 37365020.
27. Aslan AT, Balaban HY. Hepatitis E virus: Epidemiology, diagnosis, clinical manifestations, and treatment. *World J Gastroenterol*. 2020 Oct 7;26(37):5543-5560. doi: 10.3748/wjg.v26.i37.5543. PMID: 33071523; PMCID: PMC7545399.
28. The Merck manual of diagnosis and therapy 19<sup>th</sup> edition.
29. Thatipelli Ravi Chander, and Yellu Narsimha Reddy: Hepatoprotective activity of *Evolvulus alsinoides* Linn on Paracetamol induced rats. *Journal of Pharmaceutical and Scientific Innovation*, 3(4), 2014, 392-396.

30. GERTZEN O. Diet in the treatment of acute hepatitis. *Br Med J.* 1950 May 20;1(4663):1166-8. doi: 10.1136/bmj.1.4663.1166. PMID: 15420426; PMCID: PMC2037746.
31. Almeida PH, Matiello CEL, Curvelo LA, Rocco RA, Felga G, Della Guardia B, Boteon YL. Update on the management and treatment of viral hepatitis. *World J Gastroenterol.* 2021 Jun 21;27(23):3249-3261. doi: 10.3748/wjg.v27.i23.3249. PMID: 34163109; PMCID: PMC8218370.
32. Ravi Chander Thatipelli, Pradeep Kumar Sabbani, Gurunath.S : Evaluation of Hepatoprotective activity with different fractions of *Gardenia gummifera* Linn.on Paracetamol induced liver damages in rats. *Journal of Drug Metabolism and Toxicology*, 7(1), 2016, 1-7.