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STRUCTURAL DOCKING OF ANTIBIOTIC ENTECAVIR FOR THE TREATMENT OF PEDIATRIC ACUTE LIVER FAILURE BY USING DISCOVERY STUDIO

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Abstract

This research specifically focused on children who have experienced acute liver failure in the field of pediatric liver transplantation (LT). Acute liver failure in children is a complex, life-threatening illness that can either go away on its own or result in death. LT is a procedure that can save lives. Standby list mortality has decreased, as has overall prognosis, graft survival, and immunosuppression survival due to the development of technical variant grafts and subsequent immunosuppressive adjustments. Acute liver failure (ALF) is a syndrome with a variety of underlying causes, such as renal, cardiac, pulmonary, and hepatic encephalopathy, which causes a rapid loss of hepatic function. The pathophysiology of ALF, including hepatocyte necrosis, extrahepatic consequences, and hepatocyte regeneration, is significantly influenced by hepatic and circulating inflammatory cytokines. Unchecked cytokine overproduction is dangerous to the host and can have negative effects. Hepatocyte-specific injury is caused by the activation of the innate and adaptive immune systems, and T regulatory cell activity reduces this damage. The integrated stress response (ISR; e.g., PERK), p53, and HNF4 are examples of apoptotic and regenerative pathways that must be activated for the native liver to recover. Recurrent ALF is brought on by loss-of-function mutations in these pathways in response to non-hepatotropic viruses.

Introduction

Pediatric acute liver failure (PALF) affects people of all ages and has a quick onset; it typically manifests itself without any warning symptoms. It advances rapidly and has three possible outcomes: self-resolution, liver transplantation (LT), or death. Although PALF might have a variety of causes, the majority of cases up to 50% are caused by an indeterminate. Among the other etiologies include medication toxicity (particularly acetaminophen), infection, genetic disorders,

autoimmune hepatitis, oncologic processes or consequences, perfusion-related etiologies, metabolic illnesses, and genetic disorders Additionally, it might be quite challenging to predict the outcome of PALF With the limited data available to physicians to assist define a patient's trajectory, patients are occasionally treated without much awareness of the probable eventual outcome of transplantation, death, or spontaneous recovery (Crispe, 2009). 10%–15% of all pediatric LTs in the US are prescribed for acute liver failure (Palomares-Reyes *et al*., 2019) Acute liver failure (ALF) is a phenomenon with many different etiologies in which people who have never had liver disease before suffer from a liver injury that causes them to lose their hepatic function quickly. The interval between the onset of the early symptoms and the hepatic encephalopathy presentation is critical to the prognosis of these individuals. The most significant factor influencing outcomes is the etiology of ALF. There is a good understanding of differences in etiology, consequences, and treatment. ALF is largely brought on by viral infections, particularly hepatitis B, but also hepatitis A, hepatitis E, and other non-hepatotropic viruses, especially

in impoverished nations. The interval between the onset of the early symptoms and the hepatic encephalopathy presentations is critical to the prognosis of these individuals. The most significant factor influencing outcomes is the etiology of ALF. There is a good understanding of differences in etiology, consequences, and treatment. ALF is largely brought on by viral infections, particularly hepatitis B, but also hepatitis A, hepatitis E, and other non-hepatotropic viruses, especially in impoverished nations (Racanelli, 2006).

Mechanisms of acute liver failure: perspectives from liver injury

Insights from liver injury on the causes of acute liver failure. It is possible to divide the liver damage processes that cause ALF into two categories. Initially, infections and poisons directly harm cellular organelles or set off cell signaling cascade pathways that disrupt intracellular homeostasis. The blocking of these channels could offer protection from ALF. The immune system must also be able to discriminate between tissue damage and evasion, which both trigger comparable inflammatory immune reactions, to regulate the course of liver injury. The release of mediators and toxic metabolites, the metabolic implications of liver failure, and the ability of the surviving hepatocytes to replenish the liver mass are the three key elements that define the prognosis for liver failure during these processes. Excellent reviews of the direct processes causing liver damage and liver cell death have been published by several organizations. The immunological processes of liver damage, however, have not been carefully examined. Both the innate immune system and the adaptive immune system are involved in immune-mediated liver damage pathways that cause AL (Cochran and Losek, 2007)

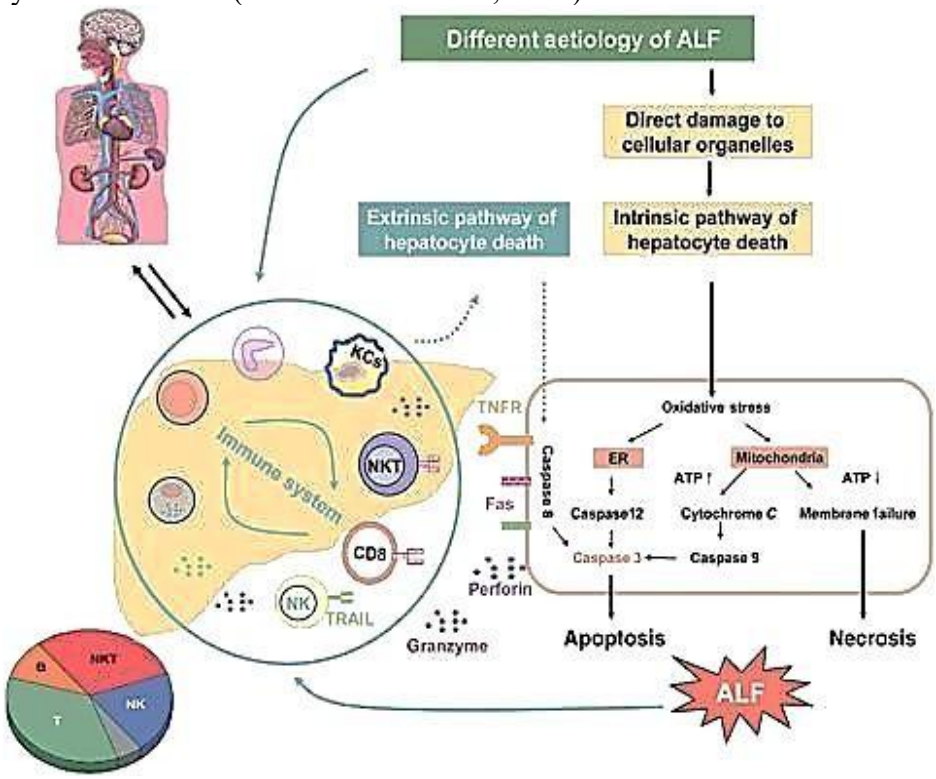

Figure 1. Insights from liver damage on the mechanisms of acute liver failure (ALF). The liver damage processes that cause ALF may be divided into two groups. The first is that pathogens or toxic substances directly harm cellular organelles or set off a cellular cascade, disrupting intracellular homeostasis. Second, immune-mediated liver damage is caused by immunological responses (both innate and adaptive), which finally converge on liver cell death pathways such as apoptosis, autophagy, necrosis, and necroptosis Doç brahim GÖREN OMÜ Gastroenteroloji (n.d.), (Shen *et al*., 2024).

Immunological mechanisms of acute liver failure

Differential features of liver immunology

The systemic circulation and the intestine, full of microbial products, environmental toxins, and external antigens, supply blood to the liver. There is mounting evidence that the liver functions as an immune organ and plays a critical role in innate immune defenses against pathogens. Kupffer cells (KCs), natural killer cells (NK), natural killer T cells (NKT), and gdT cells, as well as liver endothelial cells, are abundant in the liver. A discrete local immunological milieu is provided by the percentage of different non-parenchymal cells (Hagiwara *et al*., 2008).

Interleukin (IL)-10 and other immunosuppressive cytokines are abundant in the liver, and numerous subsets of liver cells express the inhibitory programmed death ligand 1 (PDL1) (PD- L1). Immunological paralysis and cascades of inflammatory cytokines. Septic shock is known to have ontrasting systemic pro- and anti-inflammatory patterns that lead to immunological dysfunction and organ failure (Racanelli, 2006).

The pathophysiology of ALF, including hepatocellular death, extrahepatic consequences, and hepatocyte regeneration, is significantly influenced by cytokines. Hepatocyte proliferation and regeneration are tightly tied to cytokine-mediated liver damage. Inflammatory cytokines in the liver and bloodstream influence the innate immune system in a positive feedback loop; excessive cytokine production is dangerous to the host and can have negative effects. Activation of the signal transducer and activator of transcription (STAT) and nuclear factor-kB (NF-kB)-mediated pathways have been found to quickly increase the SOCS family members SOCS1 and SOCS3, which negatively feedback for cytokine signaling, after liver damage. According to a study, SOCS1 plays significant detrimental roles in fulminant hepatitis and the prevention of hepatocytes in cases of fulminant hepatitis caused by Concanavalin A (ConA). A study shows that SOCS1 plays significant detrimental effects in fulminant hepatitis and the inhibition of hepatocyte apoptosis mediated by Fas and TNF-a in Concanavalin A (ConA)- induced fulminant hepatitis. Emerging evidence from both human and animal models shows that TNF-a is crucial to the pathophysiology of ALF. TNF-a is markedly increased in the livers and sera of ALF patients during the acute phase response (Bechmann *et al*., 2008).

Comparing ACLF to chronic hepatitis B (CHB) or healthy individuals, intrahepatic pro-inflammatory IFN-g and TNF-a expressions were considerably increased. Increased CD4 and CD8 T-cell accumulations were substantially linked with IFN-g overexpression. Increased KCs were substantially linked with upregulated TNF-a. TNF-a, IL-1, IL-6, and IL-8 have all been examined in several research that looked at the circulating inflammatory cytokines in ALF. A few studies have shown that measuring pro-inflammatory cytokines may be useful for differentiating between survivors and non-survivors due to the similarities between the levels of circulating inflammatory cytokines and the amount of systemic inflammation in ALF (Liver Failure and Artificial Liver Group & Severe Liver Diseases and Artificial Liver Group, 2006).

Presentation and diagnosis of acute liver failure

Individuals who fulfill the criteria for PALF should be thoroughly examined, with a focus on family history, previous medical history, any potential ingestions or exposures, and recent travel. Ascites, jaundice, widespread edema, heart failure symptoms, or altered mental state are all possible physical exam results. Unspecific symptoms without signs of clinical instability or end-stage liver disease may present in certain people. Depending on their age and developmental capabilities at baseline, children with hepatic encephalopathy might be challenging to evaluate. Minor symptoms like weariness, irritability, and confusion might occur, and severe encephalopathy can lead to stupor, cerebral edema,

seizures, and coma very quickly (Crispe, 2009b). A thorough metabolic panel, fractionated bilirubin, gamma-glutamyl transferase, complete blood count, serum ammonia, INR, and abdominal ultrasonography should all be included in the diagnostic workup. A liver biopsy may be used to further clarify the diagnosis, but it's crucial to remember that these procedures are prone to sampling mistakes and may not accurately reflect the histology of the entire organ. In this population, a trans-jugular approach to liver biopsy is frequently more well tolerated than a percutaneous effort because of the propensity for bleeding in the presence of hepatic synthetic malfunction (Kotoh, 2010). Although patients have a higher risk of bleeding than the general population, the risk of thrombosis may be greater than the risk of clinically important bleeding. If necessary, patients can be treated with fresh frozen plasma (FFP) and subcutaneous vitamin K supplements, albeit excessive transfusion might increase the risk of thrombosis and bleeding and no standardized transfusion procedures have been created. Overall, 5% of patients had considerable bleeding, 1% of which were intracranial bleeds. This is why all patients with acute liver failure need constant observation and daily evaluation of their general mental health (Cochran & Losek, 2007).

Table 1. An overview of the clinical findings with PALF diagnosis and treatment options.

CLINICAL MANIFESTATION	DIAGNOSIS	MANAGEMENT
Hepatic encephalopathy and hyperammonemia	**Clinical assessment, ammonia, head CT**	**Lactulose, rifaximin, consideration of CRRT**
Ascites and generalized edema	Clinical assessment, quantified on abdominal ultrasound	Diuretics
Respiratory failure	Clinical assessment and vital signs, chest X-rays	Mechanical ventilation
Circulatory failure	Clinical assessment and vital signs, echocardiogram	Pressure support
Acute kidney injury or renal failure	Serum chemistry and creatinine, urine output	Monitor fluid status, CRRT
Coagulopathy or bleeding	Coagulation panel, factor levels	Provision of FFP cryoprecipitate if bleeding or pre-procedure, vitamin K supplementation
Infection	Viral and bacterial cultures	Targeted therapy as applicable when antiviral or antibiotics
Electrolyte derangements	Serum chemistry	Maintenance of normal glucose, Na, and phosphorus levels as able; hypernatremia
		can improve intracranial
		hypertension
Cerebral edema	Head CT	Mechanical hyperventilation, mannitol, hypertonic saline

Management of PALF in intensive care units

The only effective treatment for PALF is LT. 11.2% to 12.5% of all pediatric LTs done in the US between 2010 and 2013 were for PALF. If appropriate, therapy may target the underlying cause of PALF, for as by giving acetaminophen toxicity patients N-acetylcysteine. However, most etiologies do not have a focused treatment option. As seen in the above Table, the primary goals of therapy continue to be maintaining patient stability in the intensive care unit (ICU) and treating multisystem organ failure. Patients can develop transudative fluid accumulation in extravascular compartments during PALF, which could compromise their cardiovascular health. Norepinephrine is typically a good choice of vasoconstrictor in the context of resuscitation due to its capacity to keep the central perfusion pressure constant despite fluid overload. Almost 40% of patients with respiratory failure require ventilator assistance, with low tidal volumes and increased positive end-expiratory pressure, according to the PALFSG. Continuous renal replacement treatment (CRRT) has been shown to lower blood ammonia successfully and lactate levels while enhancing transplant-free survival in patients with acute kidney damage and fluid or severe acidosis. To reduce the accumulation of ammonia, hepatic encephalopathy can be managed medically using medications such as lactulose, rifaximin, or neomycin; however, there is little evidence to support these approaches. Elevating the head of the bed, hyperventilating, using hyperosmolar treatment, monitoring the electroencephalogram, and imaging using a computed tomography (CT) scan may all be necessary for treating cerebral edema. Age less than one year at the time of presentation, the presence of Grade 4 encephalopathy, and the requirement for pre-transplant dialysis are all poor prognostic indications for PALF. No scoring system has been effectively applied to credible clinical outcome modeling, even though predictive models have been put forth (Yucel Yankol, 2016)

With an area under the curve of 88.5%–90.5%, the Liver Injury Unit (LIU) score, which utilizes peak serum total bilirubin, prothrombin time/INR, and ammonia, may predict mortality or LT by 4 weeks after patient presentation. With a concordance value (c-index) of 0.84 for predicting LT status and a c-index of 0.81 for predicting survival without LT, the LIU was able to predict LT status better than mortality in a multicenter validation trial. The Pediatric End-Stage Liver Disease (PELD) score, which is based on albumin, bilirubin, INR, the presence of growth failure, and age, was created in an effort to predict mortality before transplant in children with liver disease. While being commonly used for chronic illness, the PELD score is inconsistent in PALF and is not a suitable grading grade. Predicting patient outcomes is, therefore, still difficult. Without a validated grading

methodology, some patients who would have otherwise spontaneously recovered would be listed for and eventually get LT. (Jain & Dhawan, 2016).

PALF transplant outcomes

Death was the main result of PALF before the advent of LT, with a mortality rate of 70%– 95%. Mortality rates for the 21-day outcome dropped to 11% when LT for PALF was introduced. In contrast to individuals who underwent transplants for chronic liver disease, the long-term prognosis following a transplant for PALF could be worse. Shorter cold ischemia periods for LDLT were found in single-center research in Poland comparing results of live donor LT (LDLT) and deceased donor LT (DDLT) for PALF, with median times of 4 and 9.2 h, respectively. Reduced cold ischemia period can reduce transplant primary non-function and other organ preservation problems. The study also showed decreased waiting mortality following the use of LDLT. Urgent LDLT should be taken into account in PALF in regions of the world with restricted availability to dead donor organs (Squires *et.al*., 2006)

Biological and physiological mediators:

1. **Coagulation pathway and platelets**

Host inflammation includes activation of the coagulation cascade as a key element. Inflammatory pathways and coagulation have close connections. In addition to being triggered by the various bioactive compounds, including endotoxin, cytokines, bacterial products, and viruses, experimental data from animal models also suggests that the coagulation cascade is critical to how septic and inflammatory insults manifest. The pathophysiology of these disorders is supported by the ameliorative or preventive effects of administering neutralizing antibodies for these strong coagulants Lu *et al*., (2008). Due to its anti-inflammatory and anti-apoptotic capabilities, activated protein C, a strong anticoagulant serine protease, has been proven to have cell-protective effects. Platelet depletion lessens organ damage and intrahepatic virus-specific CTL accumulation in mice models of acute viral hepatitis. Moreover, anticoagulant therapy that reduces platelet counts without preventing intrahepatic fibrin deposition does not prevent liver damage. A key aspect of reperfusion damage in the cold ischemic rat liver model is sinusoidal endothelial cell death. One study showed that inhibiting platelet adhesion protected liver grafts from platelet-induced sinusoidal endothelial cell death after reperfusion (Hagiwara *et al*., 2008)

2. **Protein 2 similar to fibrinogen**

It is now understood that fibrin deposition and thrombosis within the microvasculature play a crucial part in the hepatic damage seen in viral hepatitis. It's significant to note that the mechanisms by which fibrin formation is produced in viral hepatitis may be mechanistically different from the traditional mechanisms of coagulation caused by mechanical stress or LPS (R. H. Squires *et al*., 2006). A new prothrombinase called Fgl2/fibroleukin is expressed on the cell surfaces of activated endothelial cells and macrophages, and it is critical for the beginning and localization of fibrin deposition. Fgl2/fibroleukin plays a crucial role in the pathogenesis of severe hepatitis B, acute-on- chronic liver failure, and fulminant viral hepatitis in mice. 21 of 23 patients (91.30%) with severe ACLF caused by hepatitis B have human fgl2 (hfgl2) identified (100–102). The c-Ets- 2 and MAPK signaling pathways are required for hfgl2 transcription to be activated by the hepatitis B virus. The bilirubin levels showed a positive connection between hfgl2 expression and the severity of liver disease. Hfgl2 and c-Ets-2 may both be possible targets for therapeutic intervention and measuring hfgl2/fibroleukin expression in peripheral blood mononuclear cells (PBMC) may be a helpful marker for assessing the severity of acute-on-CHB (Crispe, 2009)

3. **Fibronectin (FN) protein**

In acute liver damage, fibronectin (FN) is deposited in sites of hepatocellular necrosis. In contrast to quiescent hepatic macrophages, liver-inflammatory mononuclear phagocytes generate significant levels of FN. A glycoprotein called plasma fibronectin, which is produced in the liver, helps the reticuloendothelial system's Kupffer and other cells take in and eliminate circulating microorganisms and microbial metabolites by opsonizing them (RES). This opsonic chemical circulates at significantly lower amounts in ALF. Low systemic clearance of micro-aggregated albumin, an elevated risk of infection, and a greater death rate are signs of defective Kupffer cell activities, which have been linked in studies in humans to low serum fibronectin concentrations (Otsuka *et al*., 2002)

Physiological factors

Along with controlling several physiological processes, hepatic sympathetic nerves also play a role in liver damage. According to studies, the liver is crucially protected from Fas-mediated fulminant

hepatitis by nor epinephrine produced by hepatic sympathetic neurons, perhaps through pathways involving IL-6 and anti-apoptotic proteins. Modifications of autonomic nervous system activities might lead to new therapeutic possibilities and approaches for inflammatory and immunological liver disorder (J. E. Squires *et al*., 2018). Host hormones are also crucial in the development of liver disorders. The common consensus is that women are more vulnerable than men to the liver damage caused by drinking. Alcohol increased the weight and fat storage of the liver in animal models, an effect that was reduced by ovariectomy and partially reversed by estrogen replacement. Alcohol causes an increase in leucocytes that infiltrate. Ovariectomy greatly reduced and estrogen replacement dramatically restored these effects, which may be linked to an oxygen radical-mediated mechanism (Hong *et al*., 2002)

Animal models

The mechanisms of acute liver injury or failure have been studied using a variety of animal models, including those induced by chemical substances (ConA, PolyI:C, DGaLN, a-Galcer, LPS, APAP, CCl4, CpG, DMSO, CD40L), metabolic substances (ethanol, high fat, sulphatide, and NAD), infectious pathogens, and surgical models. In Asian nations, viral hepatitis is a key contributor to ALF; nevertheless, attempts to employ viruses to create animal models of ALF have mostly failed.

Table 2. Requirement for the model of acute liver failure

CONDITIONS	OBSERVATION
Reversibility	Hepatic failure should be potentially reversible to allow survival if an effective treatment is utilized.
Reproducibility	Nearly universal mortality without treatment
Death from liver failure	Selective liver damage should result in death
Therapeutic window	Time to death should be long enough to allow initiation and assessment of treatment
Minimal hazards to personnel	Toxins should present a minimal risk for laboratory personnel
Appropriate metabolism/physiology	The species utilized should have metabolic and physiological properties similar to those of humans

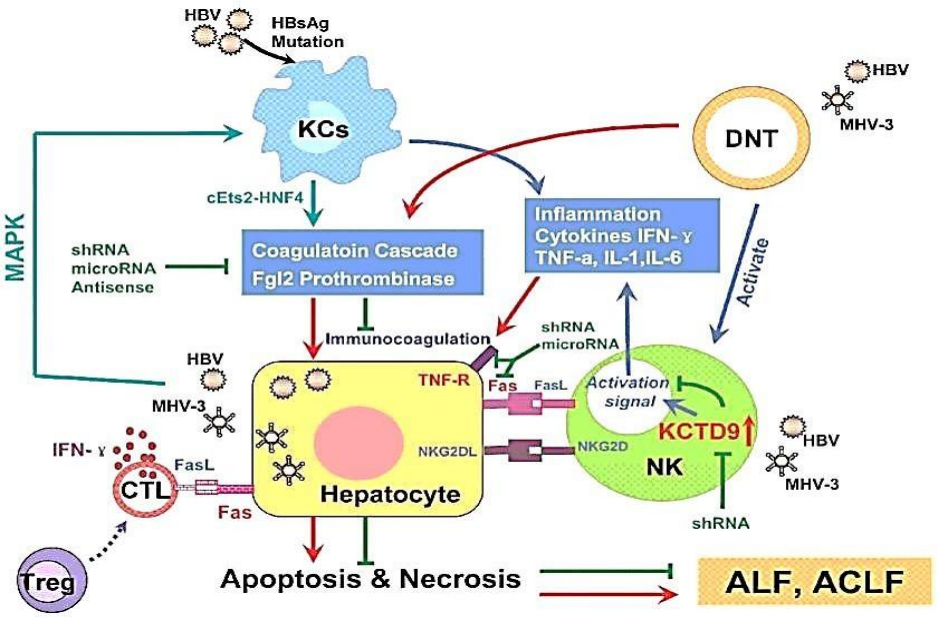

Figure 2. Proposed processes in the pathophysiology of liver failure brought on by hepatitis B virus (HBV) and murine hepatitis virus strain 3 (MHV-3). Sinusoidal Kupffer cells/macrophages and endothelial cells are activated by virus infection to produce fgl2. Interferon (IFN)-g, which is produced by activated T cells, causes resident and circulatory macrophages to express fgl2. Upon the activation of the coagulation pathway by the fgl2 prothrombinase, a fibrin matrix is created, obstructing blood flow and ultimately leading to the death of hepatocytes. Hepatocyte necrosis is a result of an increase in liver natural killer (NK) cell death caused by Fas/FasL and natural killer group 2D (NKG2D)/NKG2DL. Hepatic failure is the result of severe necrosis (Akos Végvári *et al*., 2012), (Wang and Ning, 2014).

Discovery Studio

Discovery Studio is a software best suited for simulating the structure of micro and macromolecules. It is developed and distributed by Dassault Systems BIOVIA. The product suite has a strong academic collaboration program that supports scientific research and makes use of several software algorithms developed originally in the scientific community, including CHARMM, MODELLER, DELPHI, ZDOCK, DMol3, and more (Paiva *et al*., 2022)

Applications of Discovery Studio:

The software discovery studio provides applications covering areas

- Molecular mechanics
- Molecular dynamics
- Quantum mechanics
- Ligand designing
- Pharmacophore modeling
- Structure-based drug designing
- Protein-protein docking
- Protein antibody modeling

- QSAR modeling

Specifications of Entecavir (Baraclude BMS) Drug:

Entecavir, marketed as Baraclude by Bristol-Myers Squibb, is an antiviral medication used to treat chronic hepatitis B virus (HBV) infections. As a guanosine nucleoside analogue, it inhibits HBV polymerase by blocking multiple stages of the viral replication process, including base priming, reverse transcription of the negative strand, and synthesis of the positive strand of HBV DNA. This action reduces the virus's ability to multiply and infect new cells, thereby preventing further liver damage. Structural studies, such as the one represented by Protein Data Bank entry 5XN1, have provided insights into entecavir's mechanism of action. This study examined the interaction between entecavir-triphosphate and a mutated form of HIV-1 reverse transcriptase (Q151M), offering valuable information on how entecavir inhibits viral replication. Entecavir is generally well-tolerated, with common side effects including headache, fatigue, dizziness, and nausea. Serious side effects are rare but can include lactic acidosis and liver problems. Due to its efficacy and high barrier to resistance, entecavir is considered a first-line therapy for chronic hepatitis B infection (Yucel Yankol, 2016)

Hepatitis B virus (HBV) reverse transcriptase (RT) is essential for viral replication and is an important drug target. Nonetheless, the notorious insolubility of HBV RT has hindered experimental structural studies and structure-based drug design. Here, we demonstrate that a Q151M substitution alone at the nucleotide-binding site (N-site) of human immunodeficiency virus type-1 (HIV-1) RT renders HIV-1 highly sensitive to entecavir (ETV), a potent nucleoside analogue RT inhibitor (NRTI) against HBV. The results suggest that Met151 forms a transient hydrophobic interaction with the cyclopentyl methylene of ETV, a characteristic hydrophobic moiety of ETV. We thus solved the crystal structures of HIV-1 RT Q151M: DNA complex with bound dGTP or ETV-triphosphate (ETV-TP). The structures revealed that ETV-TP is accommodated at the N-site slightly apart from the ribose ring of the 3'-end nucleotide, compared to the position of bound dGTP and previously reported NRTI/dNTP. In addition, the protruding methylene group of bound ETV-TP directly pushes the side chain of Met184 backward. Met184 is a key residue that confers ETV resistance upon substitution with smaller Ile/Val. These results provide novel insights into NRTI binding to the N- site and further provide important clues for the development of novel anti-HBV/HIV-1 RT inhibitors to overcome critical drug resistance Squires *et.al*., (2006)

Structural docking of ENTECAVIR drug

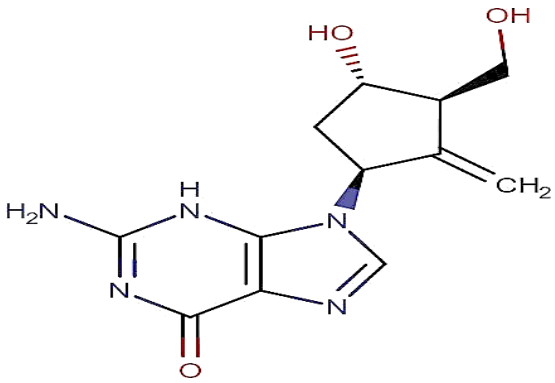

Figure 3. Basic structure of ENTECAVIR, A Self-illustrated structure using Discovery studio visualizer.

ENTECAVIR 3D Model

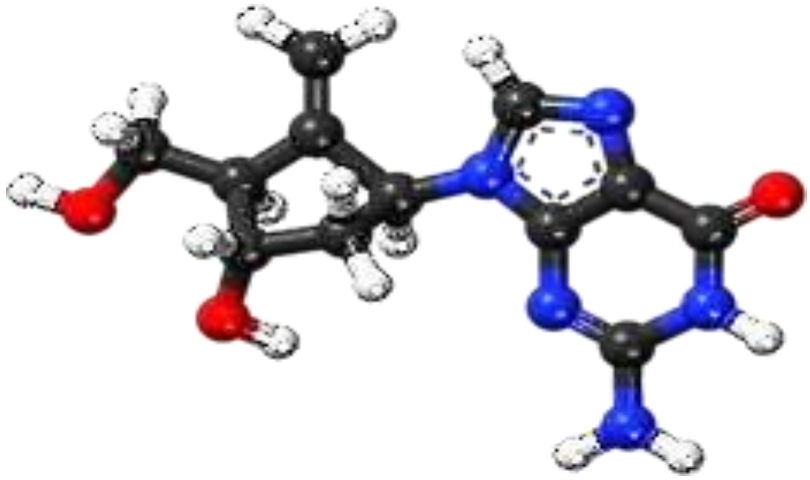

Figure 4. Entecavir structure "Ball and Stick model" A Self-illustrated structure using Discovery studio.

5XN1 structure model

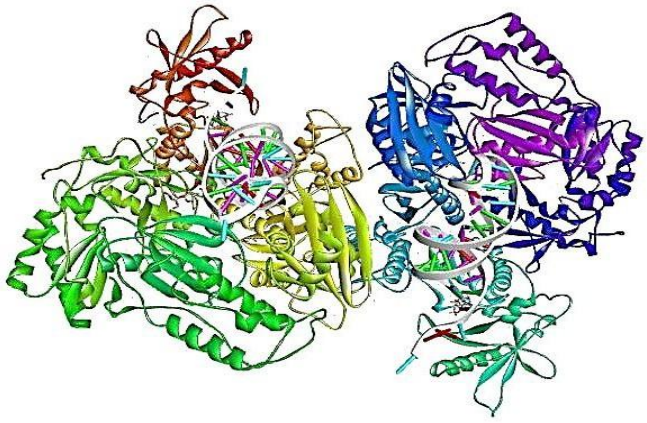

Figure 5. A complete structure of 5XN1 Protein without removing any component. A Self-illustrated structure using Discovery Studio.

Ligand binding sites

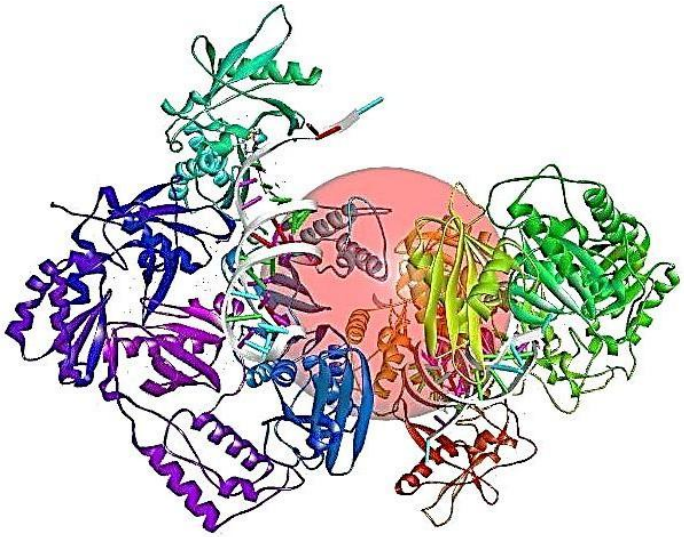

Figure 6. Ligand Receptor binding sites, created by using Discovery Studio visualizer.

Polar Hydrogen bonding

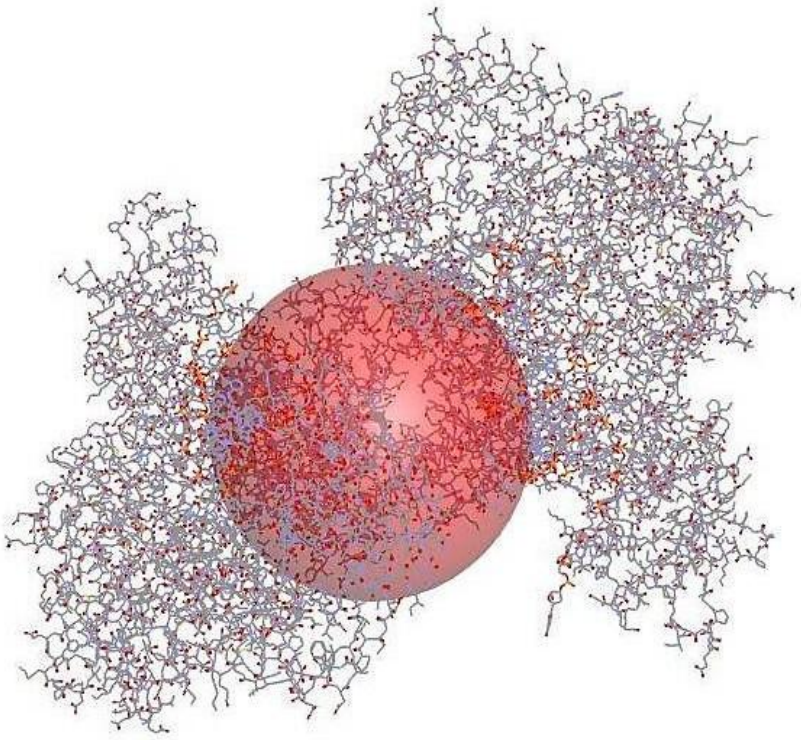

Figure 7. This Diagram shows the addition of Polar Hydrogen for docking purposes. Created using the Discovery studio visualizer.

Ligands involve in binding purposes:

There are 3 types of Ligands used in Entecavir Drugs, their names and detail given below: ET9, GOL, and MG.

1) ET9 Ligand:

Name	[[(1R,3S,5S)-3-(2-azanyl-6-oxidanylidene-3H-purin-9-yl)-2-methylidene-5-oxidanyl-cyclope ntyl]methoxy-oxidanyl-phosphory l] phosphono hydrogen phosphate
Synonyms	Entecavir 5'-triphosphate
Identifiers	[[(1~(Shen et al.),3~(Shen et al.),5~(Shen et al.))-3-(2-azanyl-6-oxidanylidene-3~(Shen et al.)-purin-9-yl)-2-methylidene-5oxidanyl-cyclopentyl] methoxy-oxidanyl-phosphoryl] phosphono hydrogen phosphate
Formula	C12 H18 N5 O12 P3
Molecular Weight	517.22
Type	NON-POLYMER
Isomeric SMILES	C=C1[C@H](C[C@@H]([C@H]1COP(=O)(O)OP(=O)(O)OP(=O)(O)O)O)n2cnc3c2NC(=N C3=O)N
InChI	InChI=1S/C12H18N5O12P3/c1-5-6(3-27-31(23,24)29-32(25,26)28-30(20,21)22)8(18)27(5)17-4-14-9-10(17)15-12(13)16-11(9)19/h4,6-8,18H,1-3H2,(H,23,24)(H,25,26)(H2,20,21,22)(H3,13,15,16,19)/t6-,7-,8-/m0/s1
InChIKey	YMBBDUCQYPKKJK-FXQIFTODSA-N

Structure of ET9 ligand

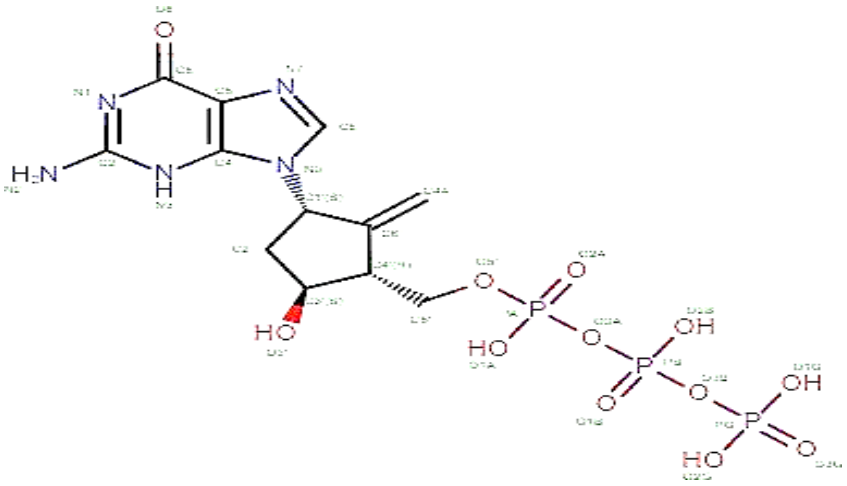

Figure 8. Structure of ET9 Ligand

2) GOL Ligand

Name	GLYCEROL
Synonyms	GLYCERIN; PROPANE-1,2,3-TRIOL
Identifiers	propane-1,2,3-triol
Formula	C3 H8 O3
Molecular Weight	92.09
Type	NON-POLYMER

Isomeric SMILES	C(C(CO)O)O
InChI	InChI=1S/C3H8O3/c4-1-3(6)2-5/h3-6H,1-2H2
In ChI Key	PEDCQBHIVMGVHV-UHFFFAOYSA-N

GOL Ligand structure:

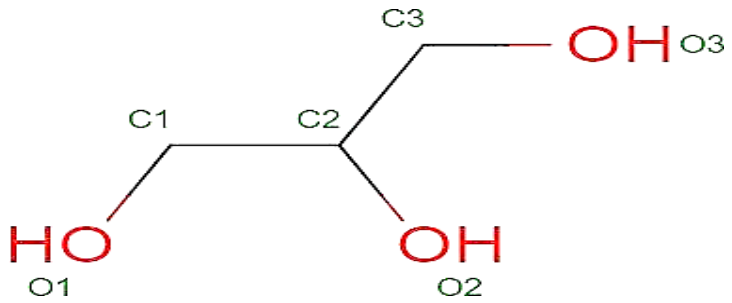

Figure 9. Self-illustrated structure of GOL using Discovery studio

3) MG Ligand

Name	MAGNESIUM ION
Identifiers	magnesium (+2) cation
Formula	Mg
Molecular Weight	24.30
Type	NON-POLYMER
Isomeric SMILES	[Mg+2]
InChI	InChI=1S/Mg/q+2
InChIKey	JLVVSXFLKOJNIY-UHFFFAOYSA-N

Crystallographic Data and Structure Determination

1. Experimental Data & Validation

Method:	X-RAY DIFFRACTION
Resolution:	2.45 Å
R-Value Free:	0.227
R-Value Work:	0.188
R-Value Observed:	0.190
Space Group:	H 3

Unit cell

Length (Å)	**Angle (°)**
a = 284.707	α = 90
b = 284.707	β = 90
c = 95.793	γ = 120

2. Software packages & purposes

Software name	**Purpose**
PHENIX	Refinement
XDS	data processing
MOLREP	phasing
Coot	model building

Transferrin:

Transferrins are glycoproteins found in vertebrates that bind to and consequently mediate iron transport (Fe) through blood plasma. They are produced in the liver and contain binding sites for two Fe^{3+} ions. Human transferrin is encoded by the *TF* gene and produced as a 76 KDa glycoprotein.

Field	**Details**
Recommended Name	Serotransferrin
Short Name	Transferrin
Alternative Names	Beta-1 metal-binding globulinSiderophilin
Aliases	PRO1557, PRO2086, serotransferrin
Related Proteins	- **Lactoferrin (LTF)** — recombinant- **MFI2 (Meltrin-alpha/MELT)** — recombinant
Molecular Weight	75,195.46 Da
Theoretical pI	6.70

Structure of transferrin:

In humans, transferrin consists of a polypeptide chain containing 679 amino acids and two carbohydrate chains. The protein is composed of alpha helices and beta sheets that form two domains. The N- and C-terminal sequences are represented by globular lobes and between the two lobes is an iron-binding site.

Structural model:

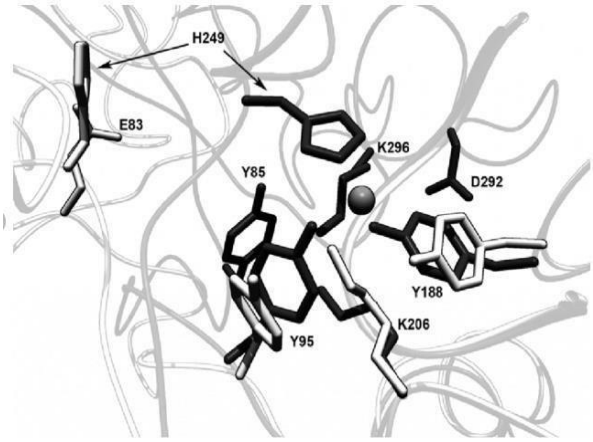

Figure 10. Molecular structure of Transferrin

3D model of transferrin from Discovery Studio

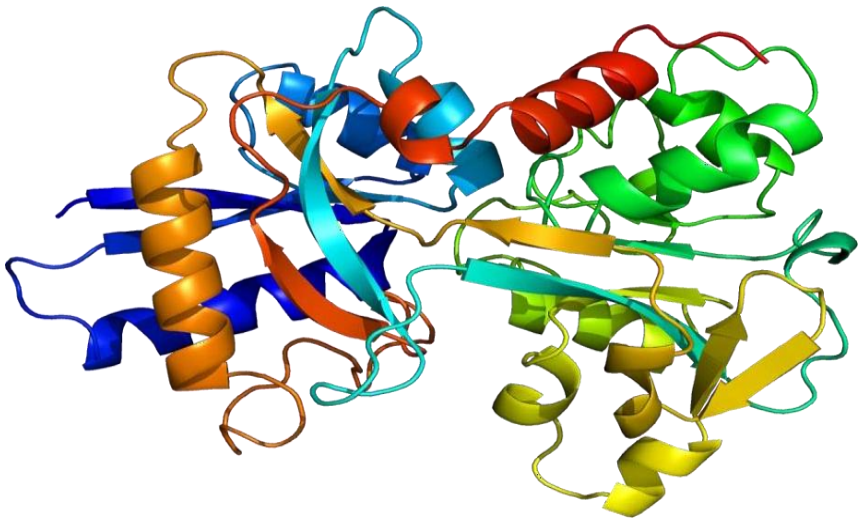

Figure 11. The molecular structure of transferrin was created by using the Discovery Studio visualizer.

Conclusion

In healthy youngsters, PALF is still an uncommon but possibly fatal disease condition. To develop trustworthy management algorithms, more characterization of its clinical course is necessary. It is still unclear how one decides when to commit to LT. Teams must balance the dangers of acute liver

failure decompensating with those of transplant surgery and prolonged immunosuppression. Regardless of the kind of graft used, data suggest better patient and total graft life after LT for PALF, and the use of technical variation grafts has considerably decreased waitlist mortality. Moreover, LDLT shortens patient wait times and could deliver better-quality organs than DDLT. It may be possible to clarify the diagnostic procedure, create prediction models, and improve the therapeutic care of these patients through research into improved methods to define the immunologic aspects of PALF. It has been argued how crucial cytokines, the innate immune system, and associated pathophysiological processes particularly coagulation factors. The difficulty is in providing a logical immunological basis for managing patients with ALF and ACLF, by either boosting or inhibiting the imbalanced immune response, given the complexity of the numerous etiologies and host immune responses. The protein transferrin plays an important role in acute liver infections. The software discovery studio has several applications in academic and research fields such as protein modeling, quantum mechanics, QSAR pharmacophore modeling, etc.

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