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CHRONOPHARMACOLOGICAL ASPECT ON IMPAIRMENT OF LIVER CIRCADIAN CLOCK AND HEPATIC DYSFUNCTION: A REVIEW

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ABSTRACT: Hepatitis B, Diabetes, Alcoholic and Non-alcoholic Fatty Liver Disease, Cholangiocarcinoma, Cholangioleiomyopathies, and other risk factors for hepatic illness are all becoming more harmful nowadays. In animals, the dysfunction of melatonin levels and an unbalanced circadian rhythm can control physiological processes and cellular mechanisms during periods of rest and activity. The Suprachiasmatic Nucleus (SCN) in the Hypothalamus of the Brain and Melatonin production in the pineal gland control circadian rhythms and clock gene expressions. The main purpose of the study is to summarise the most recent research on the molecular mechanisms underlying Circadian Rhythm, including the core clock genes and melatonin release, and their relationship to chronic liver diseases. Also covered were the future methods for studying Circadian Rhythm's Chronopharmacological Aspects for the Treatment of Hepatic Diseases.

INTRODUCTION: Circadian Rhythm is an oscillating biological cycle in which all vital physiological processes, including metabolisms, take place [1]. SCN (suprachiasmatic nucleus) is situated in the hypothalamus works as a pacemaker and that synchronizes circadian clocks through the whole body according to bright and dark phases and is mediated by autoregulatory expression of clock genes like circadian locomotor output cycles kaput (CLOCK), brain and muscle ARNT-like 1 (BMAL1) which acts as activators, period circadian protein homolog 1 (PER1), PER2, cryptochrome circadian regulator CRY1, and CRY2 as repressors [2].

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Circadian rhythms control a variety of physiological processes, and they are also disrupted and affect the liver's metabolism and circadian rhythms. By analyzing many studies, it was shown that Circadian Clock-controlled mechanisms in the liver sustain physiologicalbile acid metabolism, glucose levels, lipid metabolism, and detoxification [3].

This review highlights the fact that many genes express various levels of participation in hepatic disorders. However, melatonin treatment has shown therapeutic effects in several conditions, including hepatocellular carcinoma, diabetes, cholangiocarcinoma, non-alcoholic fatty liver disease, and alcohol-induced fatty liver diseases [4].

By reducing oxidative stress and reestablishing circadian rhythms and functioning, melatonin has the potential to be an innovative medication for liver diseases [5].

Chronological Synchronization over Hepatic Function:

Circadian Clock on Glucose Metabolism: Cryptochromes, which encode glucocorticoid receptors, that interact with G protein-coupled receptors, control hepatic gluconeogenesis, and phosphoenolpyruvate carboxykinase (CREB) controls the activation of the transcription of gluconeogenic genes [6]. According to studies, the overexpression of Cry1 in the liver of previously induced diabetic mice promotes insulin sensitivity and decreases blood glucose levels [7]. In the hyperglycemic stage, glucocorticoids which also influence the expression of Per2, are guarded against glucose intolerance in glucocorticoid therapy [8]. Through studies, it was shown that Krüppel-like factor 10 (KLF10) controls the expression of genes related to glycolysis and gluconeogenesis and that in male mice lacking KLF10, postprandial and fasting hyperglycemia resulted, whereas in female mice, it did not [9]. Bmal1 ablation in hepatocytes decreased the expression of the glucose transporter Glut2 (Slc2a2) in mutant mice **Fig. 1**, which caused a reduction in post-absorptive glucose absorption [10]. Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (Pgc1a) or Ppargc1a gene acts as a coactivator of the gluconeogenic transcription program and is generally controlled by BMAL1 [11].

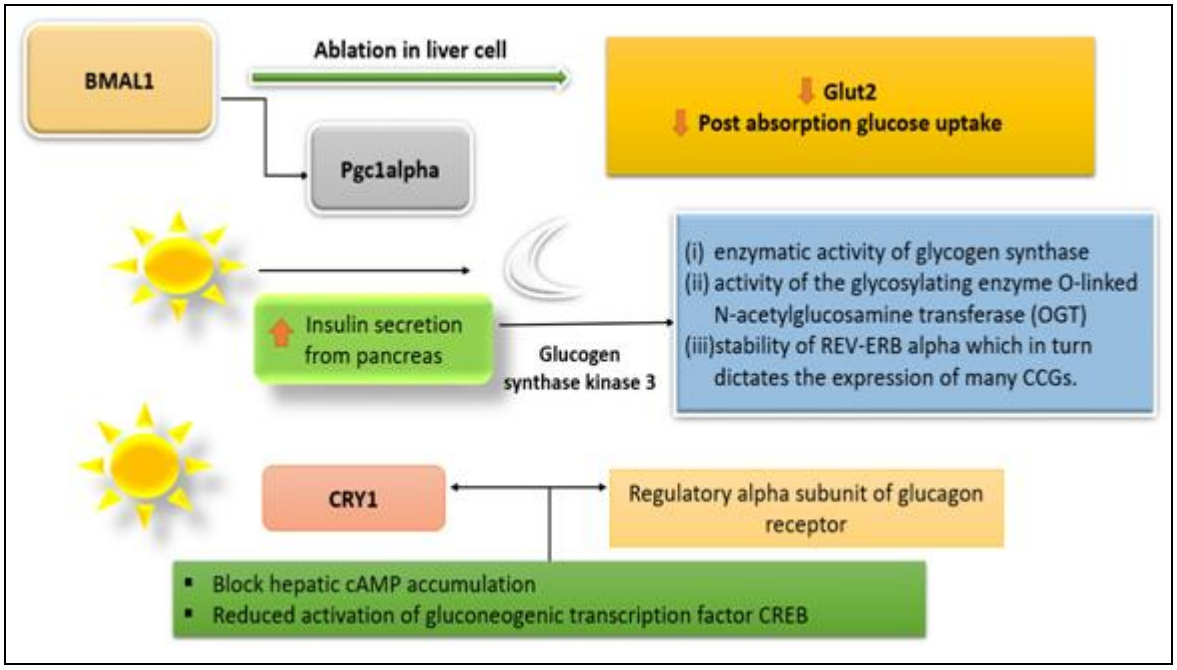

FIG. 1: GLUCOSE METABOLISM BY CIRCADIAN CLOCK

Circadian Clock on Lipid Metabolism: The Plasma levels of FFAs, TGs, and cholesterol rise after Rev-Erba/b is specifically targeted for hepatocyte ablation [12]. According to the study, ATP citrate lyase expression is higher level at the start of the active phase [13], which is when acetyl coenzyme A (acetyl-CoA) is exported from the mitochondria. According to **Fig. 2**, Cytosolic acetyl-CoA is carboxylated by acetyl CoA carboxylase to generate the malonyl CoA an essential step in fatty acid synthesis. The AMPK (PRKAA1) inactivates acetyl-CoA carboxylase by phosphorylation. The 'clock' 'temporally gates' acetyl-CoA carboxylase activity the expression of enzymes regulating b-oxidation (Cpt1/2) and ketone-body production (Hmgcs2) and their transcriptional regulators PPARα and β [14]. Several genes, including Gpat2, Agpat1/2, Lpin1/2, and Dgat2, control the many circadian-regulated phases of TG synthesis. Additionally, the Circadian Clock regulates Pnpla3 transcription and also controls the dynamics of lipid droplets [15]. A pronounced crest and trough of TG levels were seen in a study using *ad libitum*-fed mouse livers to show how the circadian clock regulates lipid metabolism throughout the rest (zt 8) and activity phases (zt 20). In a study, it was discovered that the expression of Insig2 is REV-ERB-controlled, which in turn affects the activity of SREBP1c and the Circadian Clock mechanism on lipogenesis [16].

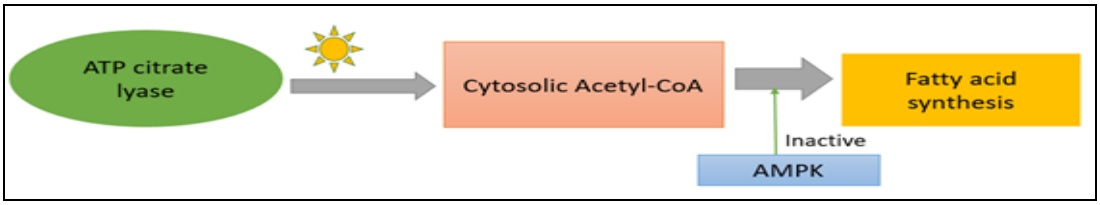

FIG. 2: LIPID METABOLISM BY CIRCADIAN CLOCK

Circadian Clock on Carbohydrate Metabolism: Circadian Rhythm of transcription factors to the promoters of targeted genes by PEPCK (phosphoenol pyruvate kinase), FBP1 (fructose-1,6-bisphosphatase), and G6PC (glucose-6-phosphatase, catalytic subunit) includes oscillations of cellular molecular clocks [17]. A high-sugar diet (HSD) was predicted and demonstrated in **Fig. 3**. To promote the expression of major transcription factors that regulate lipid, carbohydrate metabolism, SREBP1c, ChREBP, LXR, and PPAR [18]. Sucrose separately synchronizes the breakdown of the connection between the metabolic pathways and the molecular circadian clock. By influencing the post-transcriptional processes involved in mRNA stability, fructose or fructose-derived metabolites and energy status play significant roles in raising the circadian oscillation amplitudes of lipogenic genes [19]. A high consumption of sucrose promotes the development of fatty liver, hyperlipidemia, and lipogenesis, and a crucial component of this mechanism is the monosaccharide fructose [20].

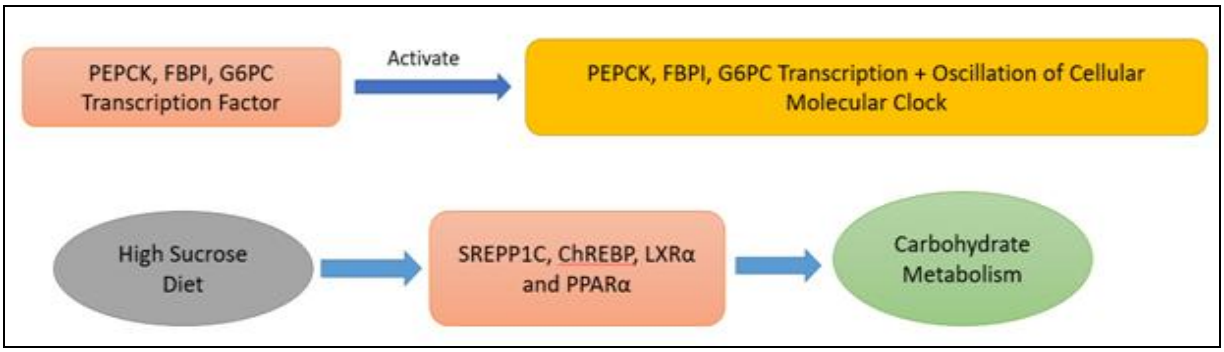

FIG. 3: CARBOHYDRATE METABOLISM BY CIRCADIAN CLOCK

Circadian Clock on Bile Acid Metabolism: In general, BAs are needed for intestinal lipid absorption. They are physiological ligands for the FXR (NR1H4) and the G-protein coupled receptor TGR5 (GPBAR1). These can activate the mitogen-activated protein kinase pathway [21]. The amount levels of TGs, cholesterol, and glucose in the liver are controlled by BAs. The nuclear receptors like FXR and SHP (NR0B2), as well as FGF15 (FGF19 in human hormone), form a transcriptional feedback loop that, as shown in **Fig. 4** [22], mainly controls the synthesis of BA. In the Bile acid synthesis pathway, the circadian transcription of cholesterol 7-hydroxylase (Cyp7a1) is driven by the expression of FXR and SHP60 in the liver and also in the intestinal secretion of FGF15 [23]. E4bp4, Shp, REV-ERBa, and other transcription factors all directly control Cyp7-1 expression [24].

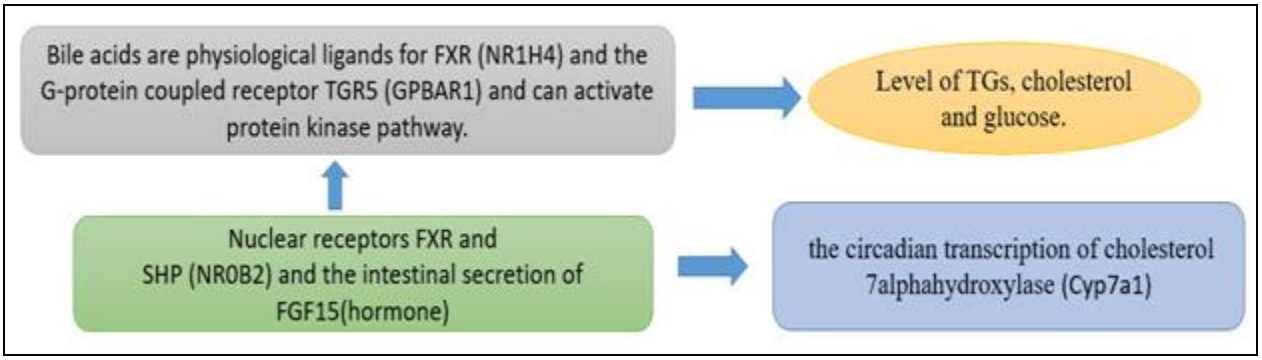

FIG. 4: BILE ACID METABOLISM BY CIRCADIAN CLOCK

Detoxification in Liver by Circadian Clock: Circadian Clock regulates practically all liver detoxification processes involving xenobiotics, including absorption, biotransformation, and excretion. In the case of humans, mornings are preferable to evenings for hepatic absorption of lipophilic medicines. The attachment of xenobiotics to nuclear receptors is the first stage of detoxification, mostly followed by transcriptional activation of detoxification pathways. Through different studies, it proved thatthe liver and other organs' circadian clock regulation in this step is controlled by the rhythmic expression levels of nuclear receptor genes [25].

- When it comes to Phase 1 detoxification, different cytochromes involve substrate oxidation and proteins that are controlled in the liver in a circadian fashion. It demonstrated that the expression peaked when animals consumed food and had the greatest likelihood of coming into contact with food that became toxic.

- In the case of the second phase of detoxification, toxins, become excretable by becoming hydrophilic by conjugating enzymes, and the excretion is triggered by transporter proteins [26].

- In the third phase of detoxification occurs at that time all classes of enzyme detoxification are rhythmically triggered through the binding of the liver-specific PAR bZIP proteins DBP, TEF, and HLF expressions [27].

Melatonin Activity on Hepatocytes: The strong antioxidant properties of melatonin help to protect the liver from non-alcoholic fatty liver disease [28]. Melatonin supplementation boosted mass and decreased blood levels of total cholesterol and triglyceride in melatonin-deficit patients brought on by radiotherapy or in surgical excision of the pineal gland for three months [29]. Oleic acid lowered the expression of the -oxidation genes PPAR and carnitine palmitoyltransferase I (CPT1). It increases the expression of genes such as SREBP-1c, FAS, and stearoyl-CoA desaturase 1 (SCD1) in HepG2 cells **Fig. 5** [30]. Melatonin therapy eliminated the consequences that prevented fat buildup. Melatonin suppresses the expression of Nuclear Receptor subfamily 4 group A member 1 (NR4A1). The activation of p53 reduces the production of cytokines, inflammation, and apoptosis [31].

A recent *in-vivo* investigation demonstrated, that the gonadotropin-releasing hormone (GnRH) secretion was inhibited by melatonin injection (1 mg/kg per day for 7 days via intracerebroventricular-implanted cannulas), that ameliorated ductular response of liver fibrosis [32]. In another study, melatonin improved liver conditions by lowering serum levels of the enzymes alanine aminotransferase (AST) and aspartate aminotransferase (ALT), and that reduced the release of proinflammatory cytokines like IL-1 and TNF in the liver by reducing oxidative stress. The administration of melatonin, which increased Bcl-2 expression and decreased BAX expression, also attenuated the development of cholangiocarcinoma (CCA) [33].

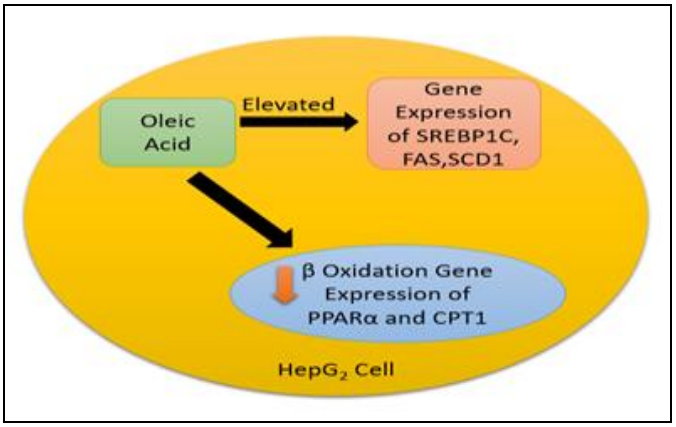

FIG. 5: OLEIC ACID ON HEPATIC CIRCADIAN RYTHM

Circadian Clock Regulation over Hepatic Disorders:

NAFLD: The spreading epidemic illness of Non-alcoholic Fatty Liver Disease (NAFLD) is currently 32.4% worldwide [34]. The pathology of NAFLD and its evolution in one research showed that itis influenced by circadian rhythms and sleep patterns. Bmal1 Clock regulates SREBP-1c, FASN, HMGCR, ELOVL, LDLr, and AACS, and acts as a cAMP-responsive coactivator of HDAC5 to control hepatic gluconeogenesis. It also drives PPAR transcription, which activates Bmal1 transcription, to manage regular lipid metabolism in the liver [35]. CLOCK can stimulate the PERK pathway. It was the cause of the activation of oxidative stress and apoptosis by inhibiting Pdia3. By increasing levels of NAD+, NPAS2 that bind to the SHP increases

its circadian expression [36]. Levels of Rev-Erb enable lipid lipogenesis by reducing HDAC3 interaction with the liver genome. Increased levels of Rev-Erbspeed up HDAC3's recruitment to the liver's metabolic genes through sleep or fasting. Through INSIG2-SREBP and LXR, which control bile acid and lipid metabolism and Rev-Erb increases circadian signalling [37]. The induction of SOD2 and GPx1 expression by Ror. Its ligands lower the hepatic oxidative stress, inflammation, and NASH in rodents [38]. By secreting IL-10, it increases M2 polarisation in hepatic macrophages, which shields hepatocytes from damage. ROR activator also triggers M2 polarity to switch in Kupffer cells, which shields the liver from developing NASH. Per2 controls the transcription of PPAR, PPAR, and Rev-Erb to control the lipid metabolism and white adipose tissue. Furthermore, KLF15 expression can be directly regulated by Per3 and Bmal1 both [39]. DEC1 inhibits PPAR expression by interacting with DNA-bound CCAAT/enhancer binding protein. InDEC1 expression is induced in the liver by LXR binding to its promoter and inhibiting phosphoinositide 3-kinase [40].

ALD: Chronic alcohol use is a spectrum of disorders that affects PER1 and CRY1 levels in the blood as well as CRY2 oscillation patterns [41]. Numerous mouse studies have shown that persistent alcohol use disrupts the circadian rhythm, which controls metabolism. Alcohol changed the hepatic circadian oscillations of gene transcription, mostly by decreasing the expression of numerous the core clock genes, including Bmal1, Clock, Cry1, Cry2, Per1, and Per2, as clock-controlled genes, including Dbp, Hlf, and Rev-ERB [42]. In mice liver fed an ethanol-containing diet, the expression of the diurnal oscillations of Bmal1, Clock, Cry1, Dbp, Hlf, Nocturnin, Npas2, Per2, Rev-erba, and Tef was suppressed. In particular, hepatic expression levels of Cry1, Per2, and Rev-erba were advanced by 1.63, 2.38, and 1.58 hr in an experiment of *in-vivo* investigation. Respectively, in mice given ethanol, it demonstrated how chronic ethanol use changed the hepatic peripheral clock [43].

Cholangiopathies: Cholangiopathies like primary sclerosing cholangitis, primary biliary cholangitis, and biliary atresia are fundamentally chronic bile duct illnesses. Melatonin's effects on cholangiocyte proliferation are often caused by binding to the MT1 receptor rather than the MT2 receptor (MT receptor) [44]. A rat model of obstructive cholestasis showed reduced biliary hyperplasia and hepatic fibrosis and alsoan increase in ductular reaction. It was detected by immunohistochemistry for cytokeratin (CK7 or CK19) and only expressed by sclerosing cholangitis. According to previous studies for increasing pineal gland melatonin synthesis through dark therapy [45]. Another research of Primary Biliary Cholangitis is characterized by a predominance of females, high titers of autoantibodies, and inflammation and damage of the bile ducts that showed cholestasis. The indicators of biliary cholangitis include (ANA) or anti-mitochondrial antibodies (AMA), aberrant lymphocyte infiltration in the portal area, or the appearance of biliary cysts [46].

In mice, injection of the type I IFN inducer polycytidylic acid, which mimics a virus, results in PBC-like liver abnormalities [47]. Neonatal cholestasis is brought on by a viral infection inadequate bile duct development, or biliary atresia [48]. According to the rotavirus strain, biliary injury, elevated blood levels of primary inflammatory cytokines, and portal lymphocyte infiltration were all caused in themodel of neonatal mice by viral injection. Cholangiocytes may get the virus that was injected [49].

Hepatocellular Carcinoma: The circadian clock regulates homeostasis of the liver organ and is a key factor inthe development of hepatocellular carcinoma (HCC), a threat to world health [50]. According to earlier research, CLOCK, Per1, and Per2 gene mRNA expression levels were higher in Bel-7404-HBx cells than in BMAL1, Per3, Cry1, Cry2, and CKI cells, a stable HBx-expressing cell lines. It is implied that HBx is involved in the expression of the circadian clock genes that lead to hepatocellular carcinoma (HCC) [51]. Huh-7 and OR6 cell lines were used as models to study the interaction between HCV infection and the expression of circadian genes. Researchers discovered that HCV genotype 1b (not genotype 3a) caused dramatic modifications in circadian genes, which were reflected inPER2 and CRY2 expression dysregulation. In OR6 cells and liver cells that were taken from HCV patients with

genotype 1b, overexpression of PER2 all resulted in a decrease in HCV RNA replicating levels and restoration of the disrupted expression pattern,a subset of interferon-stimulated genes. The PER2 was also clearly localized to the nucleus in hepaticbiopsies [52]. According to various studies, Diethylnitrosamine (DEN) dramatically disrupted circadian rhythms during resting activity and also had an impact on each animal's body temperature. Chronic jet lagwas found by generating DEN in mice to decrease the rest-activity and body temperature rhythms and enhance tumor growth, which was connected to p53 dysfunction and c-Myc overexpression. These investigations showed that it was the interruption of circadian rhythms thatprogression of liver cancer [53].

Cholangio Carcinoma: The mortality rate of cholangiocarcinoma (CCA), a bile duct cancer, is rising as the illness spreads more widely[54]. Cholangiocarcinoma growthis inhibited both *in-vitro* and *in-vivo* by melatonin dysregulation, which also throws off the circadian rhythm. By comparing the expression of the core clock genes and circadian rhythm in Cholangio carcinoma cells to the non-malignant cholangiocytes, researchers were able to determine that Per1 mRNA expression was lower in all CCA lines than in H69 cells [55]. Per1 expression was lower in human CCA biopsies compared to non-malignant tissues, while BMAL1 mRNA expression was higher in HuH-28 and CCLP-1 than in H69, but lower in CCA cells. In HuH-28 and TFK-1 cells from human CCA biopsies, BMAL1, and CLOCK expression was elevated. When Cry1 is expressed,In Non-malignant cholangiocytes and CCA cells, it went up in HuCC-T1 cells and down in Mz-ChA-1, SG-231, HuH-28, and CCLP-1 cells. In the cell lines of Mz-ChA-1, TFK-1, SG231, CCLP-1, and HuCC-T1, BMAL1 displayed a lack of circadian rhythm. The findings found that Per1 expression dysfunction was essential for controlling CCA growth [56].

Hepatitis B: Circadian rhythm genes boost the immunological response of the host cell to viral infection, and globally, infections with the Hepatitis B virus (HBV) are the main cause of liver illness and liver cancer [57]. According to previous studies, HBV infection exhibited lower levels of BMAL1 and higher levels of REV-ERB and REV-ERB transcription, which suggests that circadian rhythm gene transcription is affected by HBV infection [58]. The investigations show that REV-ERB generally binds and regulates NTCP expression and that REV-ERB activation inhibits HBV entry into hepatocytes [59]. ROR and ROR are overexpressed as a result of PPAR and PPAR gene expression dysfunctions caused by HBV. When BMAL1 binds HBV DNA, it controls the expression of the viral genome, resulting in the creation of new viral particles. Lack of BMAL1 promotes virus multiplication and, in the case of REV-ERB, inhibits the inflamed reaction [60]. The REV-ERB agonists prevent HBV replication while BMAL1 encourages virus proliferation. On the other side, BMAL1 promotes oscillations in the genes responsible for drug metabolism and toxicity, which aids in the promotion of HBV infection in hepatocytes. In the chronology study, the CLOCK gene and its downstream circadian genes are deregulated by HBV infection [61].

Diabetes: Hyperglycemia and insulin resistance or shortage are the major features of diabetes mellitus, the most prevalent metabolic disease [62]. Diabetes patients frequently have disrupted blood pressure circadian rhythms, systolic arterial pressure variation, and sleep-wake patterns [63]. In the liver, kidney, adipose tissue, vasculature, and even the submandibular gland, circadian rhythms of the mRNA levels of several clock genes, including Clock, Bmal1, Per, and Cry1/2, were disrupted [64]. Cry1/2 Ablation promotes glucocorticoid signaling, boosts gluconeogenesis, and Bmal1 rhythmic GLUT2 expression if absent, which results in hypoglycemia during a fast [65]. When glucocorticoid levels are elevated, melatonin is inhibited under aberrant LD cycles, which alter blood sugar and reduce insulin release, exacerbating the condition of glucose transporter expression and insulin resistance [66]. In a study, liver cells with knockdown of Cry1 and Cry2 produced more glucagon-stimulated hepatic glucose as well as higher blood glucose levels [67].

Chronological Therapeutic Aptitudes: Hepatic illness treatment may benefit from using the circadian clock. Research on the Rev-Erb treatment revealed that it reduced plasma levels of TGs, cholesterol, and fatty acids and caused weight loss [68]. Participation of CRY1 in the development of

new pharmacological targets for the therapy of insulin resistance andhyperglycemia was shown by different researchers [69]. SR9009 and SR9011 (REV-ERB agonists) also improved mice's metabolic endpoints [70]. TRF, which stopped obesity from rising, insulin and leptin resistance, steatohepatitis, and dyslipidemia [71]. A unique treatment for cholangiopathies involves melatonin administration and dark therapy, which helps with melatonin production. However, the impact of circadian genes on hepatocellular carcinoma immunotherapy is not fully understood [72]. In hepatocellular carcinoma therapy, targeting p21 for cell cycle activation is potentiated [73].

CONCLUSION: Recent investigations have demonstrated that a relationship between the circadian clock and metabolism was observed. The light-dark cycle activity, eating and sleeping patterns, and social pressures all have a substantial impact on human physiology and metabolism. Different types of liver disorders have been attributed to dysfunction of circadian rhythms and changes in clock gene expression. However, the introduction of melatonin may alter the circadian clock genes' levels of expression. Future melatonin intake may aim to suppress abnormal cellular communication during hepatic illnesses by targeting cell-to-cell communication between hepatic cells. But in the future, it will be crucial to research how melatonin and circadian rhythms relate to hepatic illnesses and to create effective melatonin therapies.

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