Review Article

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BRIEF OVERVIEW OF JAUNDICE AND ITS CURRENT TREATMENT OPTIONS

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Abstract

The sickness of jaundice is intricate. The cause of jaundice is a high bilirubin level in the body. Jaundice commonly manifests as skin, mucous membranes, and skin that are yellow. Pre-hepatic jaundice is caused by hemolysis of red blood cells, hepatic jaundice is caused by a problem with the liver's ability to collect, conjugate, and excrete bilirubin, and post-hepatic jaundice is caused by the obstruction of the extra hepatobiliary system. When bilirubin is metabolised, red blood cells [RBCs] go through hemolysis and release haemoglobin as a result. Heme is broken down by the heme oxygenase in the reticuloendothelial system into biliverdin and carbon monoxide. Then, biliverdin is converted into unconjugated bilirubin by the enzyme biliverdin reductase. Jaundice typically manifests as extreme weakness, fever and a headache, decrease in appetite, extremely constipated, Nausea, urine, tongue, skin, and eyes that are all yellow, dull discomfort near the liver.In the entire world, liver disease is one of the leading causes of illness and mortality. The total number of liver disease-related deaths in India reached 2.95%, per W.H.O. data released in 2017. One in five Indians may have a liver disorder.The aetiology, causes, symptoms, and combination therapy of jaundice are covered in this review study.

Keywords: Jaundice, Histology,Symptoms, Causes,Pathophysiology, Treatments.

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Introduction

The French word "jaune," which translates to "yellow," is where the word "jaundice" originates [1]. A common symptom of hyperbilirubinemia is jaundice, which manifests as a yellowish pigmentation of the skin, conjunctival membranes over the sclerae, and other mucous membranes [2].The measurement of total bilirubin > 2.5 mg/dL is considered hyperbilirubinemia [3,4].The blood carries bilirubin to the liver, where the liver processes it and excretes it in bile. A thick, yellow-green-brown fluid called bile is produced into the duodenum of the upper small intestine to help break down lipids and eliminate waste products like bilirubin and too much cholesterol. Increased red blood cell disintegration, hereditary abnormalities in bilirubin metabolism, liver disease or damage, and any disruption of bile excretion can result in jaundice [5].The pre-hepatic phase, the intra-hepatic phase, and the post-hepatic phase are the three stages in the pathophysiology of jaundice and the metabolism of bilirubin. Jaundice may result from an issue in any of these stages. The metabolic byproduct of haemoglobin in erythrocytes is bilirubin. The primary mechanism for the formation of bilirubin is the heme metabolism [6].Adult patients may experience jaundice from a variety of illnesses, ranging in intensity from benign to life-threatening. It was difficult to quickly diagnose the source of jaundice in patients who presented to the emergency room as well as to implement the right early management. Patients in intensive care units frequently get jaundice, which has a 40% incidence rate and a high mortality rate [7,8].Our red blood cells typically retire to be replaced by new ones every day at a rate of roughly 1%. The liver breaks down and discards the old ones. The body loses a large amount of the bilirubin that results in the stool. Yellow pigment accumulates in the body when the liver is unable to process too many red blood cells that are retuning. Jaundice develops when there is sufficient to be visible. Jaundice can result from the liver being overworked or damaged, from too many red blood cells dying off, or from the inability of the liver to transport processed bilirubin from the liver through the biliary system to the gut. During their first week of life, most newborns experience some jaundice. Red blood cells

can retire early during labour due to the stress of birth [particularly if a hoover is used], and newborns' livers are frequently unprepared to handle the strain. Bilirubin can build up more readily before to the arrival of mom's milk and the onset of serious stooling.Premature babies are more likely to get jaundice.It can develop due to a variety of conditions, such as blood incompatibilities, blood illnesses, hereditary syndromes, hepatitis, cirrhosis, bile duct obstruction, other liver diseases, infections, or drugs[9].Red blood cells [RBCs] undergo hemolysis during the metabolism of bilirubin, releasing haemoglobin in the process. The reticuloendothelial system's heme oxygenase converts heme into biliverdin and carbon monoxide. The enzyme biliverdin reductase then transforms biliverdin into unconjugated bilirubin. Unconjugated bilirubin binds to albumin and travels to the liver in this way. As unbound unconjugated bilirubin can breach the blood-brain barrier [BBB], it is harmful to the central nervous system[10].Though generally insoluble in water when unconjugated, bilirubin can reversibly conjugate to albumin. Bypassing the kidneys' filtration, it is delivered to the liver. In the blood, unconjugated bilirubin typically makes about 90–95 percent of the total. Bilirubin displacement from the albumin molecules in the case of hypoalbuminemia [a kind of hypoproteinemia] may result in bilirubin diffusion across the BBB. This is accomplished through the use of several medications and/or an increase in blood levels of unconjugated bilirubin. When bilirubin levels in the blood reach 15-20 mg/dL and the larger amount of bilirubin crosses the BBB, it results in bilirubin encephalopathy, also known as kernicterus [a bilirubin-induced brain malfunction] [11].Humanity considers medicinal herbs to be a gift from nature. For the treatment of jaundice and conditions including neurological, inflammatory, anthelmintic, diaphoretic, and diuretic disorders, a variety of medicinal plant parts, including herbs, shrubs, and trees, are utilised. The World Health Organisation [WHO] defines a medicinal plant as a plant that includes chemicals in one or more of its parts that can be employed for further therapeutic reasons and act as precursors for chemo-pharmaceutical semi-synthesis. The secondary metabolites of plants, which include glycosides, tannins, steroids, alkaloids, terpenoids, and essential oils, are what give plants their medicinal value[12,13].In the entire world, liver disease is one of the leading causes of illness and mortality. The total number of liver disease-related deaths in India reached 2.95%, per W.H.O. data released in 2017. One in five Indians may have a liver disorder[14].192 incidences of jaundice in total, or 2.76 cases per 1000 people, were found in India over the course of the 12-month study period. Summer and monsoon months [June to September] saw over 60% of these cases, pointing to a feco-oral mode of transmission [15].

Histology

The Babylonian Talmud describes jaundice as a symptom of "causeless hatred" and notes that it has a very long history. In the Babylonian Talmud, Sumerian Tablets, Ebers papyrus, and Ancient Ayurveda [the Indian traditional medical system], there are several historical allusions to jaundice [16].Jaundice was mentioned in Hippocrates' [460–370 B.C.] writings as well. Hepatology names like "hepatic," "liver," and "jaundice" have their roots in the French, Greek, and Sanskrit languages, respectively. The earliest Latin term for the liver was "iecur," which is probably derived from the Sanskrit word "yakrt." The term "jaundice" comes from the old French term "jalnice," which is followed by the noun "jaunice," which meaning "yellowness."Before 1800, there was not much knowledge regarding jaundice. In 1836, Addison outlined its relationship to the intake of alcohol [17–20]. Lühraman noted the prevalence of jaundice as a negative vaccination side effect in 1885. In 1908, McDonald proposed that a much smaller agent than a bacterium could be the likely cause of jaundice [21–23]. The notion that a virus was the cause of jaundice was developed in 1923. Hepatitis caused a significant number of deaths during World War II [1939–1945]. According to estimates, hepatitis caused roughly 16 million deaths during World War II. Jaundice can therefore result from a variety of liver disease disorders, such as autoimmune hepatitis, liver cirrhosis, hepatitis A, B, C, D, or E, hepatocellular cancer, or hemolytic anaemia [16,22–25].

Different Types of Jaundice

According to it's the pathology, jaundice manifests in three stages: prehepatic jaundice, which is brought on by the hemolysis of red blood cells, or erythrocytes. Post-hepatic jaundice is brought on by diminished liver function or any obstruction in the bile duct, while hepatic jaundice results from aberrant liver metabolism or liver malfunction. In addition to being a viral illness, jaundice can also be caused by various diseases that harm the liver, such as hepatitis A, B, C, and D, liver cancer, hemolytic anaemia, etc. Jaundice can also be spread by contaminated water and food-related goods, poor sanitization practises, or contaminated water and food-related products[26]. According to estimates, the hepatitis B virus infects more than two billion people each year. The Indian traditional medical system and ancient Ayurveda both demonstrate the lengthy history of jaundice [16,27]. In the Rigveda [8000 BC], biliary illness is another name for jaundice. Because medicinal plants demonstrate a higher rate of case decrease when compared to western treatments, herbal treatment is recommended for jaundice. The primary sign of this condition is the dark urine colour, while other symptoms include weakness, a high fever, nausea, loss of appetite, and vomiting. It can also result in dangerous diseases including coma, an unexpected sickness or episode of epilepsy, psychosis [a severe mental disorder], and ultimately the patient's death. A low-fat diet, plenty of water consumed as the body requires it, as well as a regular healthy diet regimen and sufficient nutrition, are typically necessary for jaundice precautions or prevention [28,29].

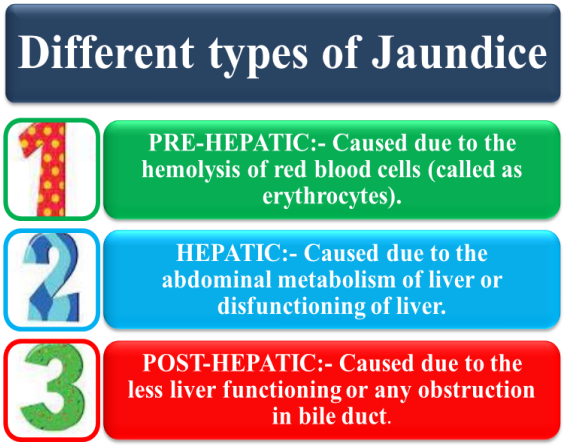

Fig.1:The various forms of jaundice according to their pathogenesis [30].

Jaundice Symptoms

Jaundice can develop gradually over time or unexpectedly. Jaundice typically manifests as extreme weakness, fever and a headache, decrease in appetite, extremely constipated, Nausea, urine, tongue, skin, and eyes that are all yellow, dull discomfort near the liver. Skin that is yellow and the white region of the eyes [sclera] may appear brown when the jaundice is more severe internal mouth colour is yellow, urine with a dark or brown colour, stools that are white or brown, Jaundice frequently co-occurs with itching [pruritis][9].

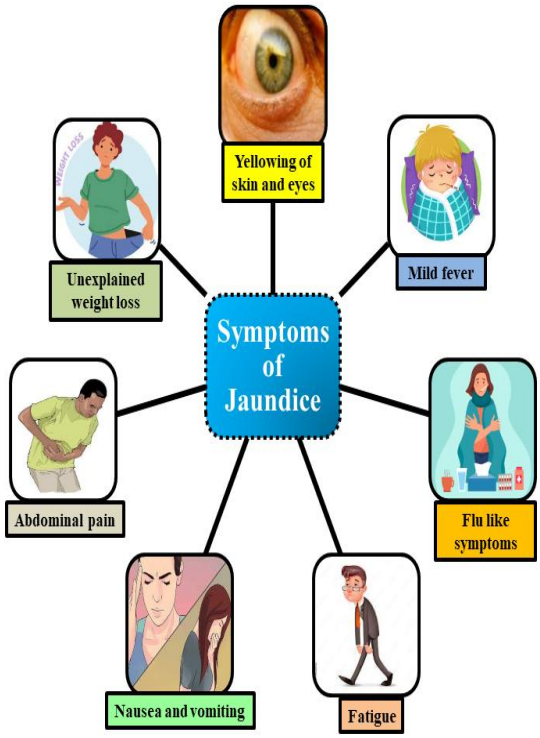

Fig.2: A few critical symptoms of jaundice.

Causes

When there is hypoalbuminemia, a form of hypoproteinemia, bilirubin may diffuse across the BBB as a result of its displacement from albumin molecules. This is accomplished through the use of several medications and/or an increase in blood levels of unconjugated bilirubin. bilirubin encephalopathy, also known as kernicterus, or bilirubin-induced brain damage, results from the greater quantity of bilirubin crossing the BBB and reaching blood levels of 15-20 mg/dL of unconjugated bilirubin. After the hepatic uptake, the bilirubin undergoes conjugation across the sinusoidal membrane within the hepatocytes. This is followed by the action of microsomal uridine diphosphoglucuronyl transferase [UDPGT], which turns the bilirubin into a water-soluble form and facilitates its excretion into the bile and by the urine[11].About 4 mg/kg/day of bilirubin is produced as a result of heme metabolism. The catabolism of erythrocytes consumes the majority of the heme moiety [approximately 80%], with the inefficient erythropoiesis and the breakdown of muscle myoglobin and cytochromes accounting for the remaining 20% [31].The most noticeable sign of jaundice is the yellowing of the skin and mucous membranes, which is caused by bilirubin's depositing and gathering of bile pigments in the blood and bodily tissues. In the instance of carotenemia, the colour expression is identical, but the bilirubin levels are normal. For the majority of babies, the pigment depositions have no impact, but in premature infants, even low doses of bilirubin have the potential to result in kernicterus. Adults typically have a normal range of blood total bilirubin concentrations of 1 mg/Dl [32,33].Jaundice in infants, also known as icterus neonatorum, has long been documented.A distinction was made between "true jaundice" and "the icteric tinge that may be seen in infants, immediately after birth" in Conspectus Medicinae Theoretico Practicae. According to the subcommittee on hyperbilirubinaemia, 10% of breast-fed infants are still jaundiced at one month old, along with 85% of preterm infants and 60% of full-term babies who appear to have developed visible jaundice. The term "physiological jaundice," which refers to newborn jaundice that becomes obvious on day 3, peaks on days 5-7, and resolves by day 14, is used to describe this disorder. Physiological jaundice is typically harmless, but serum bilirubin [unconjugated], which is neurotoxic and present in excessive amounts and passes the blood-brain barrier, can cause damage to the auditory nerve and basal ganglia and result in permanent brain damage[34–38].There are just seven new cases of this illness each year in the UK, and its complications include deafness, choreoathetoid cerebral palsy, and upgaze palsy. Jaundice's warning signs and symptoms are linked to significant liver conditions such biliary atresia, which should be treated at 6 weeks of age. It is important to remember that the condition has high social consequences. Phototherapy is the most widely used treatment for hyperbilirubinemia. However, a number of issues, including dehydration, retinal damage, bronze baby syndrome, and diarrhoea, can endanger the infant [28,38–40].

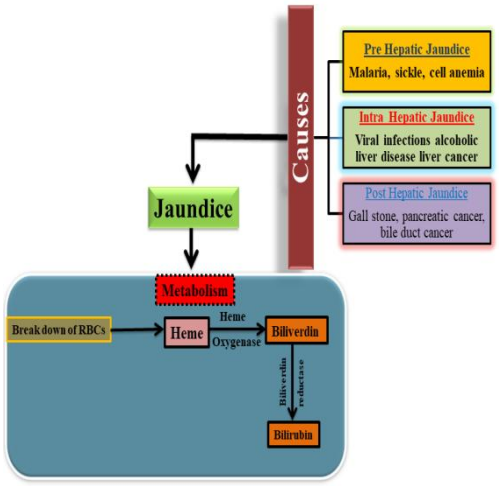

Fig.3: Jaundice's causes and bilirubin's metabolism.

Pathophysiology

There are three forms of jaundice, which include the following, according to the pathophysiology of jaundice and the metabolism of bilirubin. pre-hepatic jaundice that results from red blood cell hemolysis. Hepatic jaundice is brought on by the liver's improper handling of bilirubin metabolism and excretion. Due to the bile duct occlusion, there is hepatic jaundice. Congenital or acquired jaundice both exist. The breakdown of old red blood cells releases haemoglobin into the reticuloendothelial cells of the liver, spleen, and bone marrow, where iron, carbon monoxide, and biliverdin are released. Biliverdin is then converted by biliverdin reductase to bilirubin, which stays in the body as a waste product. Normally, the liver removes this bilirubin from the blood and, once it has been metabolised, excretes it through the urine and faeces. Jaundice is either brought on by an excess of bilirubin produced by the liver or an inability of the liver to get rid of it owing to acute liver inflammation, bile duct inflammation, hemolytic anaemia, bile duct obstruction, cholestasis, and Gilbert's syndrome[41].The average lifespan of red blood cells is decreasing, there is an increase in blood volume and haemoglobin content, and the liver enzymes are physiologically immature. A number of factors interacting to produce an unconjugated form that is not water soluble is relatively common. The conjugation reaction is catalyzed inside the hepatocyte by the bilirubin uridine diphosphate glucuronosyltransferase [bilirubin-UGT] enzyme, whose synthesis is controlled by the UGT1A1 gene. People with genetic defects in this gene consequently have poor bilirubin conjugation. Additionally, compared to adults, newborns have significantly lower levels of activity for this enzyme, which leads in conjugation that is less efficient. After conjugation, the bilirubin leaves the hepatocytes and moves to the small intestine where the gut flora converts it into stercobilin, which is then removed through the faeces[42]. In newborns, less gut flora is needed for this process than in adults, which causes a higher concentration of bilirubin to remain in the digestive tract. Theß-glucuronidase enzyme will deconjugate any remaining bilirubin in the intestine. After this, it is returned to the liver via the portal circulation for reconjugation [43].

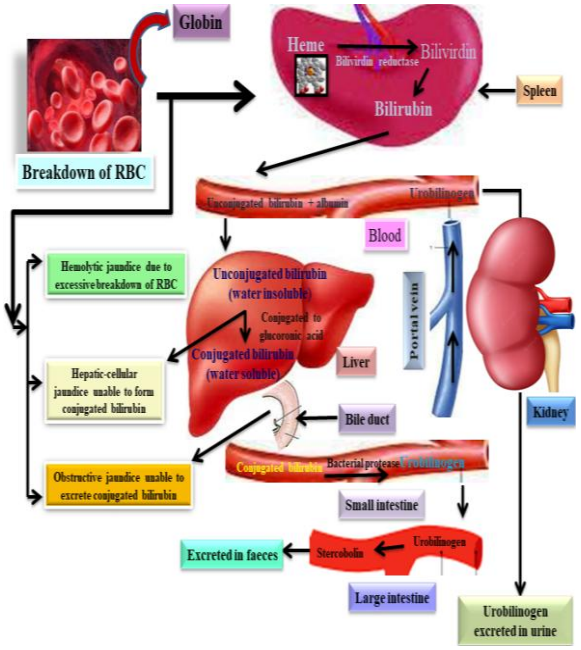

Fig.4:Jaundice's pathophysiology [44].

Options for Treatment of Jaundice

❖ Medical treatment

Although jaundice is a common symptom of a wide range of aetiologies, treatment aims to address the underlying conditions that may cause hepatobiliary injury, progressive fibrosis, and cirrhosis, which are frequently accompanied by elevated bile acid levels or abnormal metabolites. Treatment also aims to improve jaundice [by lowering serum bilirubin levels]. Improvements in nutritional status, pruritus, life quality, and the prevention or treatment of problems connected to cirrhosis are other treatment objectives [45].The most severe conditions that lead to cirrhosis and may require liver transplantation are PFICs, Alagille syndrome, and inborn defects of bile acid synthesis. There are few effective therapy options for PFICs and Alagille syndrome. Numerous medications are being research and clinical trials. Here, we'll talk about both established treatments and a number of recently created therapeutic approaches for various conditions. Ursodeoxycholic acid [UDCA] is frequently used to treat cholestatic liver disease and is efficient in reducing pruritus and improving biochemical markers[46].For PFIC2 patients with BSEP abnormalities, UDCA is an acceptable treatment choice; nevertheless, it is not optimal. Due to BSEP's failure to export UDCA from hepatocytes in animal models, UDCA may exacerbate liver damage. New medications that specifically target BSEP deficiencies must be developed. Missense mutations in BSEP/ABCB11 diminish BSEP canalicular expression and ultimately lead to cholestasis because they interfere with protein translation or intracellular trafficking. Recent research has shown that the clinically-approved pharmacological chaperone 4-phenylbutyrate [4-

PB,Buphenyl] can be employed to restore the canalicular expression of BSEP. Hayashi et al. found that 4-PB dramatically relocalizes and boosts the cell surface expression of both wild-type and mutant rat Bsep utilising MDCK II cells and SD animals [47,48].In addition to its impact on Bsep expression, 4-PB therapy in patients with ornithine transcarbamylase deficiency [OTCD] dramatically increased hepatic MRP2 and decreased serum bilirubin levels. Additionally, by re-localizing mutant BSEP to can alicular membranes, Gonzales et al. successfully restored the hepatic production of bile acids and reduced total serum bilirubin in PFIC2 patients [49,50].Steroids are a therapeutic alternative to 4-PB for increasing BSEP expression.Dexa methasone has been shown to upregulate Bsep and Mrp2 in rat primary hepatocytes at the mRNA level, and glucocorticoid therapy has been shown to increase the expression of Bsep, Mrp2, and cytochrome P450 oxidase in rat livers. Additional studies on animals and clinical trials have demonstrated that steroid therapy enhanced biliary homeostasis. For instance, bile flow significantly increased in dogs given a high dosage of hydrocortisone [5 mg/kg][51–54].In two PFIC2 patients with BSEP missense mutations, Engelmann et al. found that steroids significantly lowered bilirubin and bile salt levels in the serum as well as efficiently alleviated cholestatic itching.The reduction of hepatic accumulation of bile acids in PFIC2 patients has recently been demonstrated to be possible by blocking enterohepatic circulation. Most bile acid is absorbed by enterocytes via ASBT after it is secreted from the gallbladder into the intestine and is then returned to the liver via enterohepatic circulation. The enteric uptake of bile acid, blood total bilirubin levels, liver fibrosis, and inflammation in Mdr2 mutant mice, an animal model of PFIC3, were all significantly improved by the small molecule ASBT inhibitors SC-425 and A4250, according to two independent animal investigations[55,56].For those with deficiencies in 3-hydroxy-5-C27-steroid oxidoreductase [HSD3B7], 4-hydroxy-3-oxosteroid-5-reductase [SRD5B1, AKR1D1], and Zellweger spectrum disorders, oral cholic acid treatment is indicated. Additionally, cerebrotendinous xanthomatosis, oxysterol 7-hydroxylase [CYP7B1] deficiency, and other types of bile acid synthesis abnormalities have all been linked to improvement with CDCA [57,58].

❖ **Several herbs that treat jaundice**

▪ ***Acacia nilotica Linn.***

The scientific name for A. nilotica is Babul/Desi-kikar. In Raigarh district of Chhattisgarh, the bark, leaves, aerial section, and flower of this plant are traditionally used to cure congestion, diarrhoea, haemorrhoids, dysentery, malignancies and/or tumours, fever, TB, ophthalmia, leprosy, and menstrual irregularities [59,60].When rats are given the methanolic extract of A. nilotica, the elevated serum levels of ALT, AST, and ALP caused by acetaminophen-induced liver injury are returned to normal range levels. A. nilotica extract also shows a hepatoprotective effect against acetaminophen-induced liver damage by raising GSH levels [reduced glutathione] and lowering MDA levels [malonyl aldehyde]. Flavonoids, alkaloids, phenolics, steroids, terpenoids, saponins, and tannins are abundant in A. nilotica. As a result, this natural ingredient may be effective in the treatment of jaundice due to its ability to scavenge free radicals [61].Gallic acid and catechin found in the bark and leaves of A. nilotica have also been discovered to have preventive effects against N-nitrosodiethylamine-induced hepatocarcinogenesis [62].

▪ ***Abrus precatorius Linn***

Native to India, A. precatorius is also referred to as Gunja in Raipur and Ratti in Raigarh and the Korea district of Chhattisgarh. Traditional remedies for Tetanus, scratches, leucoderma, snake bites, fever, cough, cold, and jaundice include A. precatorius's leaves, roots, and seeds. Its paste is utilised for abortion, cancer treatment, and abdominal pain [63,64].The serum enzyme levels of alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and bilirubin are significantly reduced when hydroalcoholic extract of seeds of A. precatorius is administered orally to rats with paracetamol-induced hepatotoxicity.These outcomes were comparable to those of the silymarin reference standard. The hydroalcoholic extract's active ingredients, such as gallic acid, glycyrrhizin, and trigonelline, act as free radical scavengers, inhibiting the production of free radicals involved in the metabolism of paracetamol by microsomal enzymes, interrupting their interaction with polyester fatty acids, and reducing the membrane lipid peroxidative processes. This is a likely mechanism for the extract's hepatoprotective effects [65,66].

▪ ***Clitoria ternatea L***

The herb C. ternatea, which belongs to the Fabaceae family and is used medicinally, is also known as aparajita. The inhabitants of Chhattisgarh's Bilaspur area have long utilised the seeds of this plant as a treatment for liver enlargement and jaundice. In order to treat migraines, excessive bleeding, and child stomach pain, the juice is rubbed inside the nose. Body pains, infections, urogenital problems, anthelmintics, and an antidote for animal stings are all treated with the leaves and roots. A strong therapeutic potential exists in the methanolic extract of C. ternatea leaves to guard the liver against paracetamol-induced damage in mice. In the paracetamol-induced hepatic model, the active ingredient in the methanolic extract considerably reduces the increased levels of ALT, AST, and bilirubin. C's hepatoprotective properties. ternatea leaf may be because the extracts include phenolic components that have antioxidant and free radical-scavenging properties [67,68].The AST, ALT, ALP, bilirubin, and thiopentone-induced sleep time were all significantly reduced in the presence of ethanolic extract of C. ternatea leaves, while glutathione, catalase, and superoxide dismutase levels were significantly increased. Additionally, a study supported the hepatoprotective

effects of a methanolic extract of the C. ternatea flower against the liver toxin acetoaminophen [69,70].

- ***Baliospermum montanum [Willd.] Muell***

B. montanum, a member of the Euphorbiaceae family, is frequently referred to as Danti. Traditional uses for this plant include treating jaundice, piles, anaemia, conjunctivitis, skin diseases, snake bites, and as a blood purifier. When rats were given alcohol, chloroform, and an aqueous extract of the root of B. montanum, the high levels of biochemical parameters like SGPT, SGOT, and ALP that were raised by paracetamol significantly decreased. When compared to silymarin, the results show that alcohol and the aqueous extract of this plant exhibit significantly greater hepatoprotective effect against paracetamol-induced liver necrosis. According to reports in the literature, plants have a high concentration of phenols with strong antioxidant properties, which may account for their hepatoprotective effects [71].

- ***Chrozophora plicata Vahl***

The inhabitants of Dantewada's Bailadila reserve forest region have long used C. plicata. Rats that were experimentally drunk with CCl4, paracetamol, and thioacetamide had their serum levels of SGOT, SGPT, ALP, total bilirubin, and triglycerides dramatically reduced, while their serum levels of total protein increased. The hepatoprotective effects of the methanolic extract of the leaves of C. plicata may be due to the presence of flavonoids, alkaloids, glycosides, and lignans, which was confirmed by phytochemical screening [72].

- ***Eclipta alba [L.] Hassk***

E. alba, often called Bhringaraj, is an asteraceous plant. This plant is said to be used in folk medicine to cure jaundice, hair problems, typhoid, and dysentery. When given orally to rats with liver injuries caused by CCl4, E. alba aqueous extracts caused damage. The liver-toxicated rat's serum levels of ALT, AST, ALP, and bilirubin were considerably reduced by the plant extract. The aerial portion of this plant was also subjected to a hepatoprotective investigation on mice with paracetamol-induced hepatocellular injury, and the results revealed a strong protective impact on the mice's liver. This information supports its conventional use for liver-related diseases scientifically [73,74].

- ***Phyllanthus amarus Schum. & Thom***

P. amarus is a member of the Euphorbiaceae family of medicinal plants.Treatment of the simvastatin-induced hepatotoxic rat with the methanolic extract of this plant's seeds shown considerable hepatoprotective by returning the raised levels of SGPT, SGOT, ALP, total and direct bilirubin, serum cholesterol, and serum triglycerides to levels that are close to normal. The increased serum levels of AST, ALT, HTG [hepatic triglycerides], and tumour necrosis factor [TNF] in ethanol-induced liver injury rats are reduced to normal following treatment with an aqueous extract of the aerial portion of P. amarus. The antioxidant properties of the phytoconstituent in this plant are the likely mechanism for its hepatoprotective effects [75,76].

❖ Nutritional support

The intestinal absorption of fat and fat-soluble vitamins is mediated by bile. Defective fat and fat-soluble vitamin [vitamins A, D, E, and K] absorption is frequently seen but clinically unidentified in cholestatic liver disorders. Fat malabsorption causes calorie deficiency and stunting, particularly in young children. Patients are recommended to consume medium-chain triglyceride-containing formulations or to incorporate these oils into their diet. Multiple organ dysfunctions, including rickets, coagulopathy, and impaired neurological, immunological, and visual functioning, may be brought on by a deficiency in fat-soluble vitamins.Patients may experience deficient symptoms such as coagulopathy, osteoporosis, fracture, growth failure, and life-threatening haemorrhage without supplementation. Additionally, poor anti-oxidation, which is commonly disregarded in clinical patients, may result from deficits in fat-soluble vitamins [45].

❖ Biochemical diagnosis

Routine liver biochemistry tests include total and direct bilirubin levels, aspartate transferase levels, ALT levels, GGT levels, and alkaline phosphatase [ALP] levels for patients who may have cholestasis or jaundice. A clinical indicator for inherited cholestasis, including PFIC and inborn defects of bile acid production, is a low serum GGT level that is out of proportion to the degree of cholestasis. Biochemical analysis can be used to diagnose some diseases with metabolic characteristics. Mass spectrometry must be used to analyse diseases like inborn errors of bile acid metabolism [IEBAM] and metabolic disorders like NICCD [77,78].

❖ Genetic diagnosis

Given that many inherited hereditary liver illnesses lack adequate biomarkers, genetic diagnostics is a reliable method of diagnosis. Due to the rapid advancement of genetic analysis tools over the past 20 years, genetic tests have changed significantly. According to the patient's phenotype, direct sequencing is used in conventional genetic diagnosis for a few selected genes. Subsequently, high-throughput techniques have been created, such as a resequencing chip that identified five genes causing hereditary cholestasis in 2007 [SER PINA1, JAG1, ATP8B1, ABCB11, and ABCB4] [79].High-resolution melting analysis and denaturing high-performance liquid chromatography have both been utilised to find single-gene variations in a lot of individuals. A small number of recent next generation sequencing [NGS] panels in liver illnesses have included PFIC, in particular [45].

Conclusion and Future Direction

A general overview of jaundice, including its various kinds, symptoms, origins, pathophysiology, and combination therapy, including pharmaceutical and herbal approaches, is provided in our review articles. Our research reveals that while non-pharmacological and natural supplements

produce a reasonable outcome, take some time to act, and have no unfavourable side effects, medicine does offer some alleviation but does not completely treat the patient. To learn how to treat jaundice better, more randomised controlled researchare needed. We hope to conduct more study on jaundice in the future. With the aid of our colleagues, future study on counselling will be carried out in our country or state with the goal of assessing patients' physical and mental health and producing more precise data on jaundice and its improved therapy.

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Author Contribution

All authors are contributed equally.

Conflict of Interest

The authors confirm that they have no known financial or personal conflicts of interest that would affect the research presented in this study.

Informed Consent

Not Applicable

Ethical Statement

Not Applicable

Table.1: Current status of clinical trials on Jaundice

Drug	Mode of administration	Disease	Enrolment	Allocation/Intervention model/Masking	Official Title of the study	Status	Clinical trial	Year
BiliCam estimated bilirubin [BCB]	Interventional	Jaundice	203	N/A/ Single Group Assignment/ None [Open Label]	Bilicam Clinical Validation Study	NA	NCT03246503	2022
conventional ERCP/ Precut ERCP	Interventional	Jaundice	100	Randomized/ Parallel Assignment/ Double [ParticipantInvestigator]	Biliary Cannulation During Endoscopic Retrograde Cholangiopancreatography: Precut Versus Conventional Cannulation. A Prospective Randomized Study	NA	NCT02477228	2015
Delayed cord clamping / Cord milking/ Early	Interventional	Jaundice	400	Randomized/ Parallel Assignment/ None [Open Label]	The Risk of Hyperbilirubinemia in Term Newborns After Placental Transfusion: A	NA	NCT02625688	2017

cord clamping					Randomized-blinded Controlled Trial			
zinc gluconate / placebo	Interventional	Jaundice	294	Randomized/ Parallel Assignment/ Quadruple [ParticipantCareProviderInvestigatorOutcomes Assessor]	Effect of Oral Zinc Given Daily Between Days 2 and 7 of Life to Term or Near Term Neonates With Serum Bilirubin Levels of More Than 6 mg/dL at 24 ± 6 Hours of Life on Hyperbilirubinemia and Phototherapy.	Phase-1 & 2	NCT00692224	2008
CT Scan	Observational	Jaundice	30	NA	Multidetector Computed Tomography [MDCT] Evaluation of Obstructive Jaundice: A Cross-sectional Study From a Tertiary Hospital of Nepal	NA	NCT05919303	2023
Gene mutation sample	Observational	Jaundice	405	NA	Demographic, Metabolic, and Genomic Description of Neonates With Severe Hyperbilirubinemia	NA	NCT00383318	2008
NA	Observational	Jaundice	500	NA	A Double-blind, Randomized, Controlled Trial of Air Insufflation Versus Carbon Dioxide Insufflation During Endoscopic Retrograde Cholangiopancreatography [ERCP].	NA	NCT01321203	2011
NA	Observational	Jaundice	35	NA	Liver Echinococcosis ; Jaundice as Initial Presentation, Short and Long	NA	NCT04271176	2020

					Term Results of Surgical Treatment			
JM-105	Interventional	Jaundice	464	N/A/ Single Group Assignment/ None [Open Label]	Efficacy Study of the Draeger Jaundice Meter [JM-105] in Providing TcB Measurements to Estimate TSB in Neonates of ≥ 24 Weeks of Gestational Age Who Have and Have Not Undergone Phototherapy	NA	NCT02774434	2019
Transcutaneous Bilirubinometer/ visual assessment of neonatal jaundice	Interventional	Jaundice	430	Randomized/ Parallel Assignment/ Single [Outcomes Assessor]	Implementation of a Transcutaneous Bilirubinometer in Jaundiced Newborns: a Randomised Controlled Trial	NA	NCT01622699	2020
Blood sampling	Observational	Jaundice	180	NA	Field Evaluation of a Point-Of-Care Test for Serum Bilirubin Levels in Infants Born in a Tropical Limited-resource Setting.	NA	NCT02926131	2018
Baby Massage	Interventional	Jaundice	64	Randomized/ Parallel Assignment/ None [Open Label]	Investigation of the Effect of Massage on Bilirubin Level in Preterm Infants	NA	NCT04099602	2019
Supine position group/ Hourly position change group/ Control Group [2-hour position change]	Interventional	Jaundice	60	Randomized/ Parallel Assignment/ Single [Participant]	Effect of Repositioning Frequency on Bilirubin Level and Infant Comfort in Neonates Receiving Phototherapy	NA	NCT05692648	2023
NA	Observatio	Jaundice	535	NA	BilirubinProdu	NA	NCT01203	2019

	nal				ction in Healthy Term Infants as Measured by Carbon Monoxide in Breath		410	
Low Dose Lovastatin/Placebo / High Dose Lovastatin	Interventional	Jaundice	164	Randomized/ Parallel Assignment/Triple [Participant CareProviderInvestigator]	A Phase 2 Safety Study in Which Ischemic Stroke Patients Will be Randomized Within 24 Hours of Symptom Onset to Placebo or Oral Lovastatin 640 mg Per Day for 3 Days.	Phase- 2	NCT01976936	22017
Stent	Interventional	Jaundice	60	Randomized/ Crossover Assignment/ Single [Participant]	A Randomized Controlled Trial for Preoperative Biliary Drainage With Metal Versus Plastic Stents in Patients With Periampullary Cancer	NA	NCT02787512	2019
Transcutaneous bilirubin screening / Standard care [Visual inspection]	Interventional	Jaundice	1858	Randomized/ Parallel Assignment/Single [Outcomes Assessor]	Transcutaneous Screening for Risk of Severe Hyperbilirubinemia in South African Newborns	NA	NCT02613676	2016
G17DT	Interventional	Jaundice	41	Non-Randomized/ None [Open Label]	An Open, Multiple Dose, Single Centre Study to Determine the Antibody Response to G17DT in Patients With Advanced Pancreatic Cancer.	Phase- 2	NCT02098239	2014
Stannsoporfin Drug: Placebo Control	Observational	Jaundice	42	NA	A 4-Year Follow-up, Blinded-Outcomes Trial of Subjects	NA	NCT02033096	2019

Other: Phototherapy [as needed]					Having Received Stannsoporfin or Placebo in Clinical Trial 64,185-202			
Bilirubin estimates from Smartphone Application/Bilirubin concentration measured in standard blood samples	Interventional	Jaundice	220	N/A / Single Group Assignment/ None [Open Label]	Identification of Jaundice in Newborns Using Smartphones	NA	NCT04182555	2022
Whipple operation, Hepaticojejunostomy	Interventional	Jaundice	20	Non-Randomized/ Single Group Assignment/ None [Open Label]	Human Kidney Histopathology in Acute Obstructive Jaundice: a Prospective Study	Phase- 4	NCT01090193	2010
bilirubin concentration estimation from smartphone pictures	Interventional	Jaundice	342	N/A/ Single Group Assignment/ None [Open Label]	Evaluation of a Smartphone Based Optical Diagnostic Tool for Neonatal Jaundice	NA	NCT03007563	2020

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