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DRUG-INDUCED LIVER INJURY-DILI AND HILI IN CLINICAL PRACTICE

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1. Abstract

Drug-induced liver damage is still a problem for modern medicine. On the one hand, it is related to the polyprogression found mainly in the elderly and chronically ill, and on the other hand, to the fashion for young people to use dietary supplements and herbs. The course of DILI can range from a mild, asymptomatic, reversible increase in liver parameters to severe liver failure leading to hepatic encephalopathy, multiple organ failure and death of the patient. It is one of the most common causes of acute liver injury, accounting for 10-50% of cases and is responsible for 30-70% of cases of acute liver failure, sometimes posing a real threat to the patient's health and life.

Prevention of DILI should be based on the identification of risk factors, appropriate drug selection and patient education, avoidance of self-medication, with periodic review of patients' pharmacotherapy. Prevention of DILI requires the cooperation of the physician, pharmacist and patient, sometimes also the patient's family or carers. Knowing the initial clinical signs and systematically performing control tests of liver parameters (ALT, AST, ALP, bilirubin) can reduce the risk of severe forms of drug-induced liver damage. The article outlines the aetiology, methods of diagnosis, monitoring and treatment of DILI.

2. Keywords: DILI; HILI; Medicines; Herbs; Hepatitis; Acute Liver Failure

3. Introduction

Drug-induced liver injury (DILI) is liver damage caused by drugs (80-85% of cases), dietary supplements or herbal products - Herb-Induced Liver Injury - HILI (15-20% of cases) used in normal recommended doses, when other causes of liver damage have been excluded. The prevalence of DILI ranges from 1-20/100 000 population in developed countries and showing wide geographical variation. Unfortunately, the percentage of DILIs has been increasing in recent years, due, on the one hand, to poly-pragmasy, particularly observed in the elderly, as well as to widely available dietary supplements and herbs. The large population-based study POLSENIOR 2 showed that 51% of people aged ≥ 60 years take ≥ 5 medications, 12.4% of people aged ≥ 60 years take ≥ 10 medications, both prescription and non-prescription, 32% of people ≥ 60 years of age report using dietary supplements, while 38% of seniors with chronic pain use medications with analgesic effects.

The 2022 nationwide pilot pharmacotherapy review of medicines showed that Polish patients in their senior years are usually lost in their own pharmacotherapy, do not understand the rules of taking individual medicines and often take medicines that interact with each other in an adverse way. The second problem diagnosed after unnecessary pharmacotherapy turned out to be adverse drug reactions, followed by drug interactions and patients' non-compliance with doctors' and pharmacists' recommendations. Of the drugs that cause DILI, the most common are antibiotics, which account for 46% of DILI cases in the US, dietary supplements, NSAIDs, tuberculostats, cytostatics, drugs used for cardiovascular disease and preparations used for metabolic disorders, neurological disorders, drugs with hormonal effects and drugs used in biological therapy.

The number of liver injuries caused by herbs and supplements may also be underestimated due to a lack of complete epidemiological data, as not all cases of DILI and HILI are reported, often herbs and supplements are used spontaneously without the knowledge and control of the physician, and on the other hand, some diagnostic difficulties - the similarity of clinical symptoms with other conditions - may contribute to a lack of proper diagnosis and reporting. In developed countries, it is estimated that HILIs account for 15-20% of DILI cases, while in developing, Asian countries, where the tradition of natural, herbal medicine is firmly established - Chinese medicine or Ayurveda, HILIs may account for a higher proportion of liver damage. In Chinese studies, HILI accounted for about 25-30% of DILI cases [1-4].

4. Participants and Methods

4.1. There are two mechanisms of action of hepatotoxic drugs

- **A direct hepatotoxic effect (intrinsic DILI)** that depends on the dose of drug taken and is predictable. It is characterised by a short latency period (time from drug intake to onset of symptoms of liver damage), usually between 1 and 8 weeks. E.g. paracetamol.
- **The phenomenon of idiosyncrasy (idiosyncratic DILI)** i.e. a not entirely unexplained rare hypersensitivity to the hepatotoxic effect of a given drug. Here, the latency period can vary widely - from 1 week to even 12 months! The clinical picture is varied and the effect in this mechanism is not dose-dependent and is difficult to predict. Here, the hepatotoxic effect occurs as a reaction immunological or metabolic [1,5-7] [Figure 1].

In contrast, with regard to HILI, liver damage is usually due to toxic compounds present in herbs or supplements.

4.2. There are four mechanisms of action of herbal hepatotoxic supplements

- Direct toxicity - Plant constituents have a direct damaging effect on hepatocytes.
- Idiosyncratic response - Depends on individual patient response.
- Toxic metabolites - Formed by metabolism in the liver, e.g. by cytochrome P450 enzymes.
- Drug interactions - Herbs can affect the metabolism of other substances, potentiating their toxicity.

4.3. Herbs that are most likely to cause HILI include

- St John's wort (Hypericum perforatum),
- Kava kava (Piper methysticum),
- Chinese herbs (e.g. Traditional Chinese Medicine preparations):
- Ephedra (ma huang),
- Paeonia (peony) and other mixed ingredients,
- Preparations with aloe vera (Aloe vera),
- Herbs containing pyrrolizidine alkaloids
- Tussilago farfara (coltsfoot), Senecio (senescence),
- Slimming preparations,
- Garcinia cambogia, green tea in high doses,
- Herbs used in detoxification containing untested blends with a high risk of idiosyncrasy [8-11].

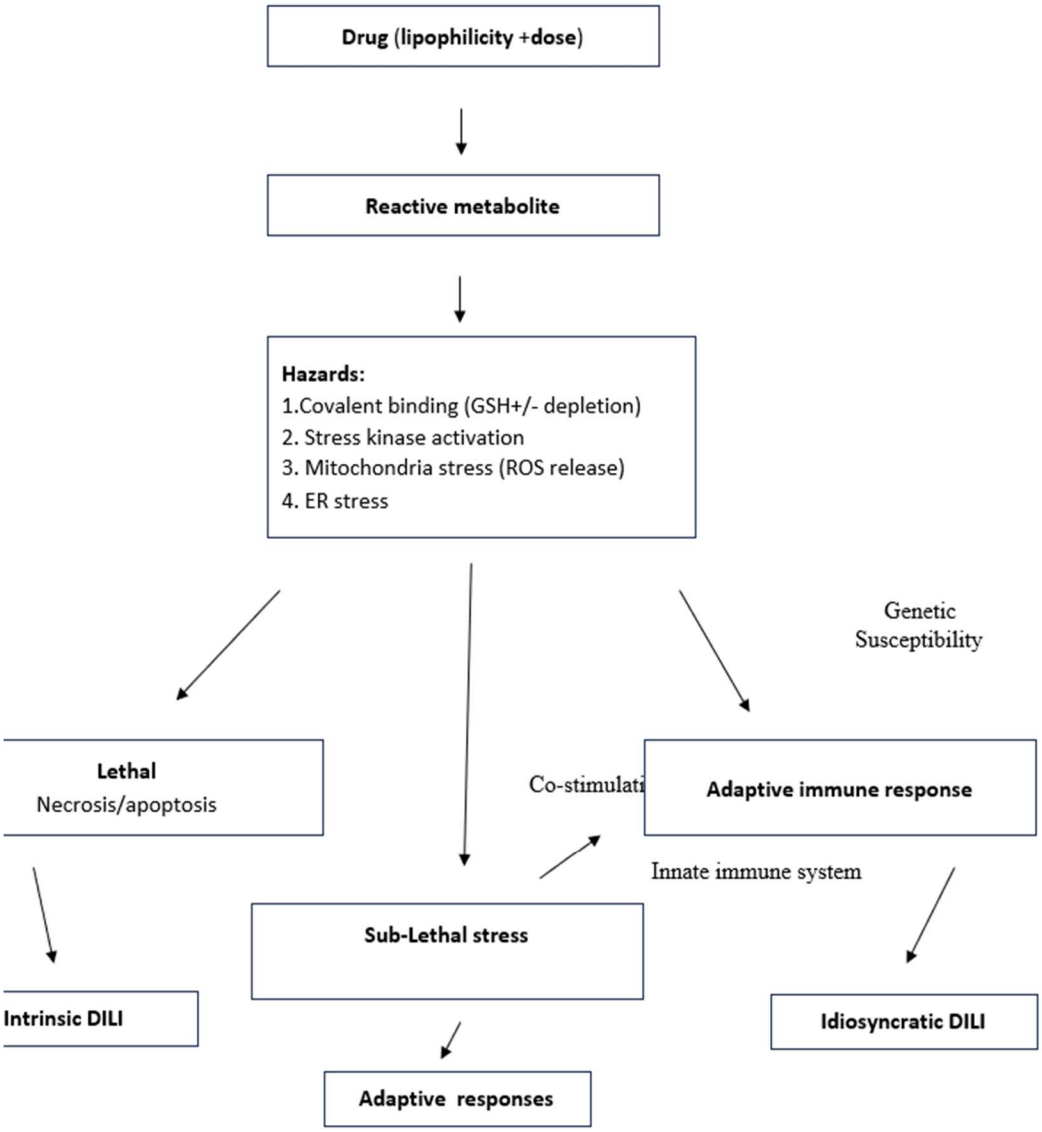

Figure 1: Relationship between intrinsic and idiosyncratic DILI.

The potential hepatotoxic effects of drugs depend on several factors that depend on the drug itself, as well as on the patient and environmental factors.

4.4. Drug-dependent factors include

- The unit and daily dose of the drug, sometimes, for some substances, also the cumulative dose,
- Pharmacokinetic profile,
- Risk of drug interactions, especially of drugs metabolized by cytochrome P450,
- Ability to cross-react between drugs.

4.5. Patient-dependent factors include

- Age,
- Gender,
- Pregnancy,
- Obesity,
- Degree of nutrition,
- Genetic profile,
- Comorbidities.

4.6. Among the environmental factors mentioned are

- Use of polytherapy,
- The use of dietary supplements,
- Smoking,
- Alcohol consumption [1, 12-15].

5. Clinical Manifestations of DILI

Most cases of DILI are asymptomatic and laboratory tests performed at the time show elevations in liver parameters - Alat, Aspat, GGTP, ALP, bilirubin. Some patients may report a feeling of faintness, fatigue, lack of energy, non-specific epigastric pain, a feeling of discomfort, entrapment in the right lower abdomen. Occasionally there may be a darkening of the urine. Some patients may experience fever, rash, diarrhea, yellowing of the skin and sclerae. Some of the symptoms of DILI will pass spontaneously, once the drug is discontinued. Some require the administration of hepatoprotective and hepato-regenerative drugs. Some progress to chronic liver damage [Table 1]. In contrast, some can lead to acute liver failure, which is a real threat to the patient's life, characterized by a rapid deterioration of liver function, accompanied by hemorrhagic diathesis and hepatic encephalopathy [1,6, 15-18].

5.1. Clinical forms of DILI

- **HEPATOCELLULAR (Parenchymal) -** Primarily involves damage to liver cells, characterized by the following abnormalities in laboratory tests: ALT ≥ 5 GGN or when the ratio of ALT to ALP activity ≥ 5.
Example drugs: Paracetamol (acetaminophen), isoniazid.

- **CHOLESTATIC** - Involves impairment of bile flow, leading to bile accumulation, characterized by the following abnormalities in laboratory tests: ALP ≥ 2 GGN or when the ratio of ALT to ALP activity < 2.
Example drugs: Amoxicillin-clavulanate, anabolic steroids.

- **MIXED** - Features a combination of hepatocellular and cholestatic injury patterns, when the ratio of ALT to ALP activity varies between 2 and 5.
Example drugs: Phenytoin, sulfonamides.

These types are typically distinguished using the **R-value**, calculated as:

R = ALT (x ULN) / ALP (x ULN)

- **R > 5**: Hepatocellular DILI
- **R < 2**: Cholestatic DILI
- **R = 2–5**: Mixed DILI

Type of liver injury	Drugs
Cholestatic	amoxicillin with clavulanic acid, erythromycin, clopidogrel,ace inhibitors (angiotensin-converting enzyme inhibitors), anabolic steroids, azathioprin, oral contraceptives, carbamazepine, chlorpromazinetricyclic antidepressants
Hepatocellular	acetaminophen, diclofenac, ibuprofen, naproxen, ciprofloxacin, ketoconazole, protease inhibitors, sulfamethoxazole with trimethoprim, rifampicin, tetracycline, valproic acid, pyrazinamide, trazodone, isoniazid
Mixed	clindamycin, statins, amitriptyline, sulfonamides, phenytoin, protease inhibitors

Table 1: The most common hepatotoxic drugs.

Some forms of DILI can mimic Autoimmune Hepatitis (AIH), presenting with serological or histopathological features characteristic of AIH (diclofenac, halothane, indomethacin, infliximab, methyldopa, minocycline, nitrofurantoin and statins). It can also manifest as secondary sclerosing cholangitis, with changes typical of Primary Sclerosing Cholangitis (PSC) visible on Magnetic Resonance Cholangiopancreatography (MRCP) or liver biopsy (amiodarone, atorvastatin, amoxicillin-clavulanate, gabapentin, infliximab, 6-mercaptopurine, sevoflurane and venlafaxine). DILI may also take the form of granulomatous hepatitis, characterized by the presence of granulomas in histopathological examination (allopurinol, carbamazepine, methyldopa, phenytoin, quinidine and sulphonamides), or lead to acute fatty liver (amiodarone, didanosine, stavudine, valproate and zalcitabine) or drug-associated fatty liver disease (methotrexate, 5-fluorouracil, irinotecan, tamoxifen, corticosteroids, lomitapide and mipomerson) [Figure 2 and Table 2].

DILI can also cause ductopenic syndrome - vanishing bile duct, with chronic cholestasis (azathioprine, androgens, amoxicillin-clavulanate, carbamazepine, chlorpromazine, erythromycin, estradiol, flucloxacillin, phenytoin, terbinafine and co-trimoxazole). Some drugs can cause Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome (anticonvulsants - carbamazepine, phenytoin and phenobarbitone, minocycline, allopurinol, abacavir and nevirapine). Additionally, prolonged use of certain medications can sometimes cause liver tumors, such as hepatocellular adenoma or carcinoma (anabolic androgenic steroids and oral contraceptives) [1, 19-21].

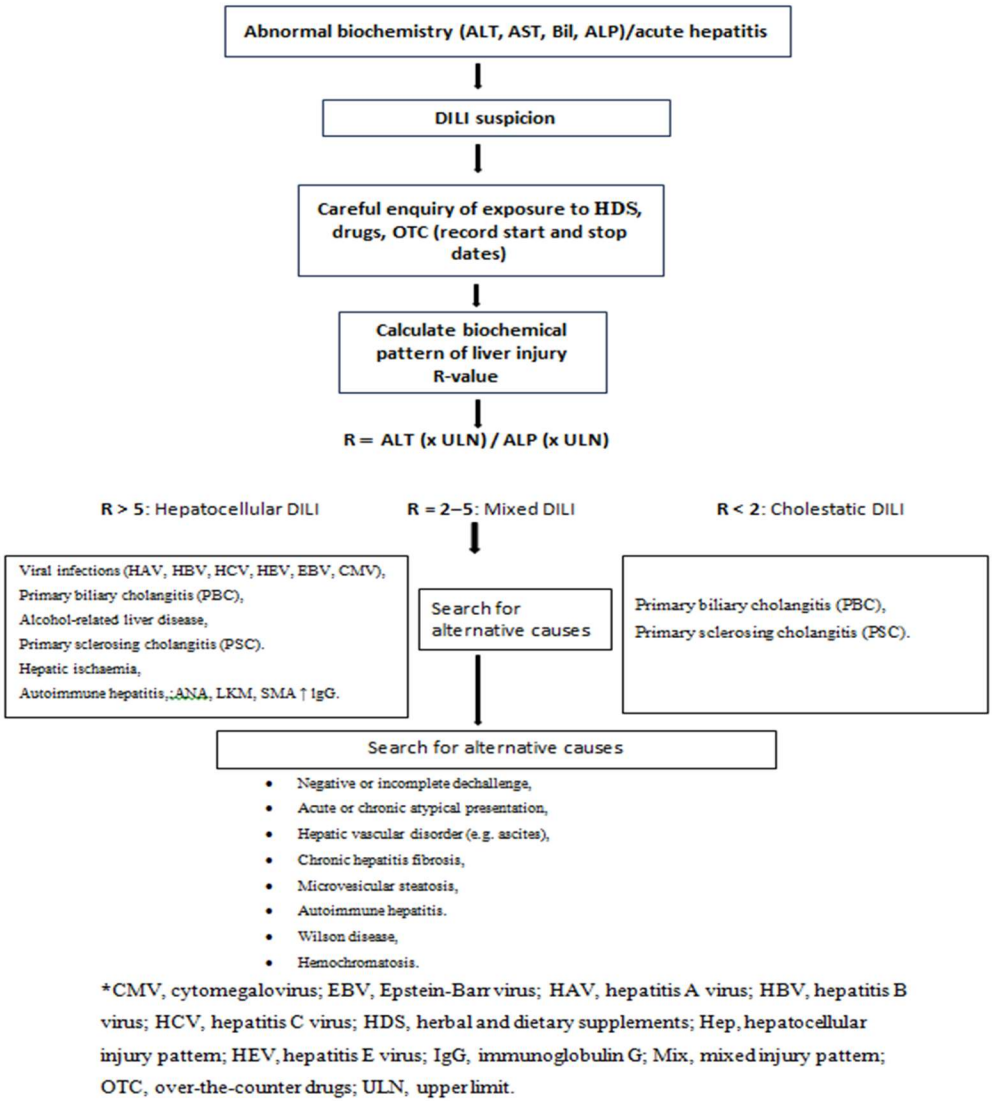

Figure 2. Algorithm for management in suspected DILI.

Category	Severity	Description
1	Mild	ALT ≥5 or ALP ≥2 and TBL
2	Moderate	ALT ≥5 or ALP ≥2 and TBL ≥2 ULN, or symptomatic hepatitis
		ALT ≥5 or ALP ≥2 and TBL ≥2 ULN, or symptomatic hepatitis and 1 of the following criteria:
		- INR ≥1.5,
3	Severe	- Ascites and/or encephalopathy, disease duration < 26 weeks, and absence of underlying cirrhosis,

		Other organ failure due to DILI.
4	Fatal/ Transplantation	Death or liver transplantation due to DILI.

*ALP, alkaline phosphatase; ALT, alanine aminotransferase; INR, international normalized ratio; TBL, total bilirubin, ULN, upper limit of normal.

Table 2: DILI severity classifications International according to DILI Expert Working Group.

6. Treatment of DILI

Most often there is no causal treatment for the DILI component, only N-acetylcysteine is used in paracetamol poisoning and levocarnitine in valproic acid poisoning. The prognosis of patients with DILI is generally favorable-most patients experience regression of clinical and laboratory changes after discontinuation of the hepatotoxic drug. Thus, in patients with parenchymal liver damage when ALT > 3-fold above normal with a bilirubin concentration of more than 3 mg/dl (10% risk of death), the suspected drug should be discontinued immediately. In patients without jaundice and with an ALT increase < 3 times normal, the drug dose can only be reduced with continued monitoring of transaminase activity. It is therefore advisable to monitor the patient, especially according to the severity of the clinical symptoms and the abnormalities of the laboratory tests, in order to qualify for hospitalization and inpatient treatment. In the case of features of acute liver failure in the course of DILI, it is always necessary to hospitalize the patient, monitor his or her clinical condition and possibly qualify for assisted treatment with plasmapheresis or albumin dialysis and, in some cases, qualify for liver transplantation.

6.1. When the drug should be discontinued in the case of DILI

- ALT or AST>8 GGN
- ALT or AST > 3 GGN with bilirubin > 2 GGN or INR > 1.5
- ALT or AST > 3 times above normal accompanied by fatigue, nausea, vomiting, right lower back pain
- ALT or AST >5 GGN persisting for more than 2 weeks.

Drugs and dietary supplements used in the treatment of drug-induced liver damage include ornithine aspartate, timonacicum, silibinin, silymarin, flavone derivatives derived from milk thistle, soy phospholipids or UDCA - ursodeoxycholic acid. The use of this type of medication, especially over-the-counter ones, should always be consulted with a doctor. In cases of cholestatic or parenchymal-cholestatic liver damage, the return of laboratory indices to normal may be accelerated by the administration of UDCA in doses of 500-750 mg/day. Cholestatic mechanisms often contribute to DILI, even if the clinical picture is hepatocellular. Therefore, the mechanisms underlying the benefit of UDCA in cholestatic disease may be applicable in hepatocellular and mixed DILI. Steroid treatment is used in selected clinical cases, especially when the liver damage is immunological in origin or there are features of severe hepatitis. Usually 20 to 40mg of prednisone or methylprednisone per day is used. Once improvement is achieved, the dose is gradually reduced over several weeks. When treated with steroids, it shortens recovery time and reduces the risk of progression of liver damage [1, 22-26].

6.2. Acute liver failure in the course of DILI

Acute liver failure is a sudden, rapid deterioration of liver function in a patient previously without liver disease, leading to hepatic encephalopathy and coagulation abnormalities within < 26 weeks of symptom onset - INR ≥ 1,5. The clinical signs of acute liver failure are the occurrence of the so-called triad of symptoms: disturbance of consciousness, jaundice, coagulation disorders (haemorrhagic diathesis). Other symptoms include hepatomegaly, liver shrinkage, hypotonia, hyperventilation, epileptic seizures, diarrhoea, fever, rash, cerebral oedema - intracranial hypertension, brainstem intussusception,hypoglycaemia, acidosis, alkalosis, acute kidney injury, septicaemia, coagulopathy - bleeding, multi-organ failure [1,23-27].

6.3. Drugs most likely to cause acute liver failure

- Paracetamol
- Other Nsaids: Indomethacin, Phenylbutazone, Gold Salts
- Drugs Used for General Anaesthesia: Halothane, Isoflurane
- Psychotropic Drugs: Mao Inhibitors, Tlpd
- Antiepileptic Drugs: Phenytoin, Valproic Acid
- Antitubercular: Isoniazid, Rifampicin, P-Aminobutyric Acid
- Antibiotics And Chemotherapeutics: Tetracyclines,
- Cotrimoxazole, Ketoconazole
- Others: Labetalol, Methyldopa, Disulfiram, Androgens.

6.4. Indications for liver transplantation in acute liver failure according to King's College criteria

- **Paracetamol**

1. Arterial blood pH < 7.3

Or 1+2+3

1. Hepatic encephalopathy 3rd or 4th degree,
2. INR > 6.5 or prothrombin time > 100 s,
3. Creatinine > 3.4 mg/dl (300 umol/l),

- **Other causes than paracetamol poisoning:**

1. INR > 6.5 or prothrombin time > 100 s,

Or > 3

1. Age < 10 years or > 40 years
2. duration of jaundice before encephalopathy > 7 days,
3. INR > 3.5 or prothrombin time > 50 s,
4. bilirubin level > 18 mg/dl (300um/l),
5. Hepatitis not A or B, drugs [28].

6.5. Alternative liver replacement methods used in DILI

Extracorporeal liver function support (ELS) methods help to keep the patient with acute liver failure alive until recovery, prolonging survival time until donor acquisition and liver transplantation, so-called 'bridging treatment'.

- MARS - molecular adsorbent recirculation system - source of external albumin.
- Prometheus - source of albumin from patient plasma,

- SPAD - single pass albumin dialysis (combined with veno-venous haemodiafiltration),
- biological systems - cell therapies (HepatAssist, Extracorporeal Liver Suport Device, etc.).

7. Conclusion

In summary, DILI can affect any patient regardless of age. However, it is more common in the elderly, those with multimorbidity, those taking multiple medications and obese, alcohol-abusing patients, We can more often expect DILI in people with previously diagnosed liver diseases - overlap syndromes. It seems necessary to take a thorough history of diseases, medications, stimulants, dietary supplements and herbs used. Periodically perform a drug review of patients, including the dosage of drugs and dietary supplements and herbs taken. The clinical course of DILI can range from asymptomatic to acute liver failure. Fatigue, discomfort in the right lower abdomen or skin pruritus may be common first symptoms. Therapeutic management should firstly discontinue or reduce the dose of the potentially hepatotoxic drug, assess indications for hospitalization, recommend follow-up, consider hepatoprotective/hepatoregenerative treatment e.g. UDCA, in some cases GCS. Cooperation between the doctor, pharmacist and the patient, as well as the patient's relatives, patient education, knowledge of the causes, early clinical signs of DILI, and periodic testing of liver parameters form the basis for preventing the dangerous complications of drug-induced liver damage [1,2,6,29].

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