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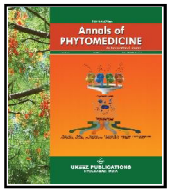

Review Article : Open Access

The indispensable role of herbs and other treatment strategies against gallstones

V. Lalitha◆, G. Shila, P. Amsa*, T. Prabha, R. Saravanan and R. Madhavan*****

Department of Pharmacology, Nandha College of Pharmacy, Erode-638052, Tamil Nadu, India

** Department of Pharmaceutics, Nandha College of Pharmacy, Erode-638052, Tamil Nadu, India*

*** Department of Pharmaceutical Chemistry, Nandha College of Pharmacy, Erode-638052, Tamil Nadu, India*

**** Department of Community Medicine, Nandha Medical College and Hospital, Erode-638052, Tamil Nadu, India*

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Abstract

Gallstone also known as cholelithiasis, is a hepatobiliary illness that results in a solid deposit in the gallbladder. It represents a significant epidemiologic burden worldwide. It may be symptomatic or asymptomatic, affects women more frequently than men. Biliary pain is the primary symptom; it later develops as cholecystitis. The currently available novel non-surgical treatments, such as oral dissolution therapy using drugs like ursodiol and chenodiol are used, but has some draw backs, like a low capacity to dissolve gallstones, and treatment takes years. Surgical procedures such as cholecystectomy (gallbladder removal) have a high treatment cost and can result in complications such as digestive problems. Drugs are already available to dissolve stones, but none exist to prevent gallstones. Therefore, complementary and herbal therapies are required to dissolve as well as prevent gallstones. In this review, information that was published in the literature between 1990 and 2022 is gathered from databases like Science Direct, Scopus, PubMed and Google Scholar. Plants and other treatment modalities used against gallstones were discussed in this review. Preventative and dietary medicinal plants like *Trigonella foenum-graecum* L. and *Allium sativum* L. have been used for centuries to cure gallstones. Plants were widely used because they are culturally accepted, efficient, safe, and have fewer side effects than commercial drugs due to their non-invasive, painless, and affordable procedure that favorsmany patients.

1. Introduction

Gallstone disease, also referred to as cholelithiasis, is one of the most common digestive diseases and a major cause of abdominal morbidity throughout the world, and it may manifest with or without overt symptoms (Pradhan *et al*., 2009). A Florentine pathologist named “Antonio Benivenius” first documented the condition, cholelithiasis in 1507. A mummified Egyptian priestess was also found to have many gallstones. Globally, cholelithiasis is a prevalent condition that affects 10% - 20% of the global population and 11% of the US general populations. Gallstones affect 20% of adults in affluent nations on average, and the morbidity rate has been rising by 0.60 - 1.39% annually (Diehl *et al*., 1990). With a significant frequency in the younger age range, incidence is four times as common in women as in men (20-30 years). Its incidence in India is believed to be between 2 to 29%, with northern states having a higher frequency than southern states (Pimpale *et al*., 2019).

Gallstones, which have been a concern for humans for many years, are abnormal lumps made up of a solid mixture of calcium bilirubinate, cholesterol crystals, proteins, and mucin. According to their makeup, gallstones are classified as cholesterol stones, pigment stones, or mixed stones. The difficulties in determining symptom status and discriminating between two groups (symptomatic and asymptomatic) of patients must be stressed. Gallstone-related biliary tract pain may manifest in the upper right quadrant of the abdomen.Various types of indigestion (abdominal bloating, belching), stomach discomfort, and pain in the right shoulder are common in patients with gallstones, although these symptoms appear to be experienced by people without gallstones just as frequently. However, abdominal pain from other sources can be characterized by the patient in a way that makes it difficult to differentiate it from biliary pain, especially if the patient is not examined when the pain first starts (Friedman, 1993). Children with cholelithiasis may or may not have symptoms. Gallstones in adults are often cholesterol or mixed stones; however, in children, hemolytic disorders including sickle cell anemia, thalassemia, and hereditary spherocytosis are more common and lead to the formation of pigment stones (Rajoo *et al*., 2022). Ultrasonography makes the diagnosis of gallstones quite simple. The primary basis for diagnosing symptomatic gallstones is, medical history (Berger *et al*., 2000).

Gallstones have been linked to extra biliary cancers as well as cardiovascular problems. Although, gallbladder cancer is thought to be primarily caused by gallstones, it is a rather uncommon illness (Ruhl and Everhart, 2011). Although, the process of gallstone development involves several factors, it is unquestionably linked to a family history of the condition, diabetes mellitus, pregnancy, obesity, considerable weight loss, and hemolytic disorders. Biliary colic, acute cholecystitis, and gallstone pancreatitis are frequent causes of surgical treatment for cholelithiasis (Freitas *et al*., 2006). Laparoscopic cholecystectomy is the procedure of choice for treating

Corresponding author: Dr. V. Lalitha

Associate Professor, Department of Pharmacology, Nandha College of Pharmacy, Erode-638052, Tamil Nadu, India.

E-mail: sasiikv@gmail.com

Tel.: +91-9789948682

symptomatic gallstones because of its widespread use and acceptable safety (morbidity less than 5.0%, death less than 0.2%) among patients and healthcare professionals (Festi *et al*., 2009). Drug dissolution therapy: for patients who reject surgery or pose a poor risk, oral bile salts have been used to dissolve gallstones for more than 30 years. Both chenodeoxycholic acid (chenodiol) and ursodeoxycholic acid (ursodiol) are known to dissolve gallstones over 6 months to 2 years period. Only a small percentage of patients with symptomatic cholesterol gallstones are candidates for bile salt therapy. Patients who require immediate treatment for acute cholecystitis or common bile duct stones should not use it. Following the cessation of oral bile salts, gallstones frequently recurred.

2. Types of gallstones

The fundus, corpus, and infundibulum are the three anatomical components that make up the gallbladder, a thin-walled sac that is often located between both hepatic lobes (Behar, 2013). A complex chain of circumstances that precipitates insoluble materials in the gallbladder leads to the formation of gallstones. Bile salts, which are physiological detergents that can solubilize lipids, help the intestine to absorb dietary fats and enable the liver to expel relatively insoluble molecules from bile. Gallstones develop when the liver produces insoluble lipids and inorganic salts that are unable to dissolve in bile (Donovan, 1999). The composition of gallstones is affected by age, diet, and ethnicity. Gallstones can be categorized based on the chemicals they contain (Portincasa *et al*., 2006). Humans can develop three types of stones: cholesterol stones, pigment stones (often known as black and brown stones), and mixed stones. The incidence of mixed stones was 80.7%, while cholesterol and pigment stones constituted 13.5% and 5.8%, respectively, in northern India.

2.1 Cholesterol stones

The primary reason isobesity; it contains 80% of cholesterol. The color of cholesterol stones ranges from pale yellow to dark green, brown, or chalk white. They are oval, typically solitary, between 2 and 3 cm long, and frequently have a small, black patch in the middle (Sharma *et al*., 2019).

2.1.1 Pathogenesis of cholesterol gallstones

Cholesterol gallstones are caused by cholesterol super saturation of bile, gallbladder hypomotility, and kinetic, pro-nucleating protein factors that are crucial for the development of cholesterol gallbladder stones (Figure 1).

2.1.1.1 Cholesterol supersaturation

Phospholipids, primarily phosphatidylcholine, and bile salts are combined to form micelles that make cholesterol soluble in bile (lecithin). When the solubility of cholesterol is exceeded (cholesterol saturation index > 1), cholesterol precipitates and forms multilamellar vesicles, which fuse and may coalesce into solid crystals. Thus, hypersecretion of cholesterol or hyposecretion of bile salts or phospholipids contributes to the supersaturation of cholesterol in bile (Marschall and Einarsson, 2007).

2.1.1.2 Gallbladder hypomotility

This is the ensuing long-term stasis of lithogenic bile and appears to be the most important factors in stone formation. Gallstone recurrence was found to be more strongly correlated with the severity of gallbladder emptying impairment due to a prolonged stasis of lithogenic bile in the gallbladder, which provide more time for cholesterol crystallization and aggregation into macroscopic gallstones (Chen *et al*., 2014). Gallbladder hypomotility occurs while using oral contraceptives, in postoperative states or burns, and in diabetic people (Reshetnyak, 2012).

2.1.1.3 Mucin hypersecretion and chronic gallbladder wall inflammation

Both are regarded as key contributors to the etiology of cholesterol gallstone diabetes (GD). The development of inflammation in GD is also significantly influenced by bacterial infection (Gaby, 2009).

2.1.1.4 Elevated estrogen levels

The elevated estrogen is frequently linked to a marked rise in hepatic production of biliary cholesterol during pregnancy. Bile becomes more lithogenic, causing cholesterol supersaturation. Furthermore, excessive levels of estrogen and progesterone may decrease gallbladder motility by preventing the smooth muscle's ability to contract, resulting in gallbladder stasis. Pregnant women who have these anomalies are far more likely to develop gallstones and biliary sludge (Bari *et al*., 2014).

2.1.1.5 Other causes

Include intestinal bile salt metabolism, cholesterol crystal formation due to physical factors (pregnancy, obesity, rapid weight loss, intestinal hypomotility, diet hyperlipidemia), bacterial infection, genetic risk factors, medications that affect cholesterol homeostasis (such as octreotide and clofibrate therapy), and spinal cord injury (Donovan,1999).

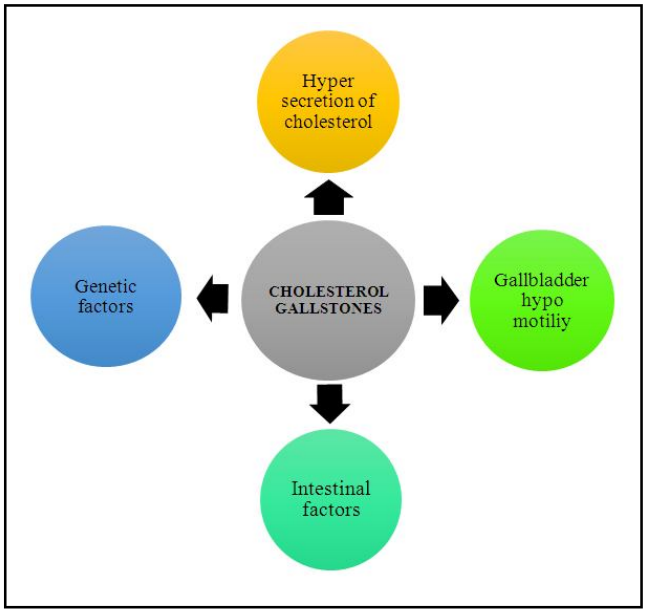

Figure 1: Pathophysiology of cholesterol gallstones.

2.2 Pigment stones

It contains less than 20% of cholesterol. They are dark, abundant, and typically tiny stones, often known as "black pigment" or "brown pigment" stones. They are principally made of calcium (calcium phosphate) salts found in bile and the insoluble bilirubin pigment polymer (Sharma *et al*., 2019).

2.2.1 Pathogenesis of pigment gallstones

- **Brown pigment stones:**The stones that form primarily in the bile ducts are brown in color. They largely consist of calcium salts of unconjugated bilirubin and different concentrations of protein and cholesterol. Brown pigment stones are linked to chronic bacterial bile duct infections caused by *Bacteroides* spp., *Escherichia coli*, and certain parasites. According to Venneman and Erpecum (2010), these bacteria produce beta-glucoronidase, phospholipase A, and bile acid hydrolase, which increase levels of unconjugated bilirubin and bile acids, as well as stearic acids, which can interact with calcium to form stones.
- **Black pigment stones:** They are produced by the gallbladder's sterile bile. Gallbladder motility issues are not pathogenesis-related (Venneman and Erpecum, 2010). They result from elevated levels of unconjugated bilirubin in cirrhosis, alcoholism, or intravascular hemolysis, as well as elevated levels of conjugated bilirubin. Free radial polymerization of calcium bilirubinate causes the formation of black pigment stones. They do not have any connection to bacterial diseases. Biliary stasis is implicated in both cholesterol and pigment stone production, and chronic hemolytic diseases or biliary infections play a role in the pathophysiology of pigment stones (Cao and Eslick, 2018).

2.3 Mixed stones

It contains 20-80% cholesterol and looks like sticky mud, which is numerous, faceted, and mixed with both cholesterol and pigment are also known as "brown pigment stones". Calcium carbonate, palmitate phosphate, bilirubin, and various bile pigments are additional prevalent components (calcium bilirubinate, calcium palmitate, *etc*.). They frequently show up on radiographs due to their calcium concentration. They often develop as a result of bacterial infections of the biliary tract (Sharma *et al*., 2019).

3. Risk factors

Gallstones are more likely to happen in women who are fertile and have a history of gallstone illness in their families (Marschall and Einarsson, 2007). Using oral contraceptives, taking estrogen replacement drugs, losing weight quickly, getting older, being overweight, having type 2 diabetes, dyslipidaemia (high triglycerides and low HDL(high density lipoprotein) serum cholesterol), hyperinsulinaemia, and living a sedentary life are all risk factors for gallstones (Portincasa *et al*., 2006). A high body mass index (BMI) is also linked to a higher rate of gallstone disease (Stender *et al*., 2013).

- **Age:** Gallstones are more common as people get older, becoming much more common beyond the age of 40. This is hypothesized to be caused by a decrease in the rate-limiting step for the synthesis of bile acids, cholesterol 7-alpha hydrolase, which results in an increase in biliary cholesterol super-saturation. Although, it is observed that the prevalence of gallstone disease in children and adolescents under the age of 16 is rising, it is still quite uncommon.
- **Obesity:** It is considered that obesity raises HMG-CoA (hydroxy methylglutaryl-coenzyme A) reductase activity, which raises the likelihood of cholesterol gallstone development by increasing biliary cholesterol production.
- **Prolonged fasting:** Gallbladder bile appears to be supersaturated in the fasted state, and fasting causes gallbladder stasis.
- **Dietary factors:** The incidence of gallstones is increased by excessive caloric consumption, diets high in total fat and cholesterol, or refined carbs, while protective dietary factors include high fiber intake, vegetable protein, nuts, calcium, vitamin C, coffee, and alcohol (Cao and Eslick, 2018). Often, attacks occur after a particularly fatty meal and almost always happen at night and after drinking.
- **Ethnicity and gender:** One of the most important risk factors for gallstone disease is gender. Due to their naturally higher estrogen levels, multiparty use, or usage of estrogen-based oral contraceptives, women are typically more susceptible to cholelithiasis than males.
- **Lipid profile**: The main component of gallstones, cholesterol, is a form of lipid that is predominantly produced in the liver and only eliminated through the biliary system. Due to the complicated and multivariate nature of gallstone production, cholelithiasis is challenging to treat. Hypersecretion of cholesterol, supersaturation, and other factors have all been linked to the development of cholesterol gallstones. Although research has been done to determine the connection between lipid levels and gallstones, the results are still up for debate.
- **Physical activity:** It indicates that being physically active prevents the development of cholelithiasis, but being inactive raises the risk.
- **Diseases**: Gallstone disease frequently co-occurs with the metabolic syndrome, dyslipidemia, diabetes, and insulin resistance or hyperinsulinemia. Gallstones may also become more likely in those with chronic hepatitis C virus (HCV) infection. Gallstones, especially those with a black colour, are at increased risk for development in people with Crohn's disease and liver cirrhosis.
- **Alcohol and smoking**: The risk of gallstone disease has been demonstrated to be inversely correlated with alcohol use. By lowering bile cholesterol saturation and increasing HDL cholesterol levels, moderate alcohol use may reduce the incidence of cholesterol gallstone disease. Alcoholic cirrhosis is a significant independent risk factor for gallstones, and severe alcohol misuse enhances the chance of (pigment) gallstone synthesis (Pak and Lindseth, 2016).

4. Signs and symptoms

The majority of gallstone sufferers are asymptomatic, that is, without symptoms. These are called "silent stones", and these gallstones may not need to be treated (Njeze, 2013). Gallstone management must now be decided between surgical removal and expectant management as asymptomatic gallstones are more frequently found (Gibney, 1990).

Most frequently, patients with symptomatic stones report recurring biliary pain episodes. The impaction of a stone in the cystic duct is likely the cause of biliary pain, which is a constant right upper quadrant or epigastric pain. They may experience severe abdominal pain in the upper right side, often accompanied by nausea and vomiting, that worsens over 30 minutes to several hours. Additionally,

referred discomfort between the shoulder blades or below the right shoulder area (Boas' sign) may be experienced by the patient. Attacks almost always take place at night and frequently after a very fatty meal (Njeze, 2013). Narcotics work quickly to relieve the pain, which is minor compared to renal colic pain. Most persons with gallstones would not experience any symptoms. Only patients with symptoms need to be treated. Consequently, it is vital to combine symptoms with clinical judgement (Traverso, 1993).

Nausea, vomiting, bloating or belching, fever, jaundice, and right upper quadrant soreness during pain are additional symptoms and indicators of biliary pain. Bloating, fatty food intolerance, and vague pain in the right upper quadrant are all symptoms of flatulent dyspepsia. With most patients, whose symptoms cannot be solely attributed to the stones, the existence of gallstones is probably unrelated (Egbert, 2016). Multiple stones have reportedly been associated with more symptoms and problems than single stones (Muhrbeck, 1995).

5. Complications

The most common complications of gallstone disease are acute cholecystitis, acute pancreatitis, ascending cholangitis, gallbladder perforation or empyema, gallbladder cancer, and gangrenous gallbladder. Mirizzi syndrome and cholecystocholedochal fistula are both signs of the same condition that causes a gallstone to get stuck in the neck of the gallbladder. This blocks the bile duct and causes jaundice (Saif and Kawas, 2002).

Acute cholecystitis, the most typical of these, is characterized by inflammation of the gallbladder, persistent, severe upper abdomen pain, discomfort, fever, and leukocytosis (Diehl,1992). Gallstone migration and obstruction in the distal common bile duct caused pancreatic inflammation, which in turn caused bile to reflux into the pancreatic duct and limit pancreatic production. Gallstone pancreatitis is mild and self-limiting in about 80% of cases (Alemi *et al*., 2019). However, 20% of instances can be serious and result in major morbidity and mortality. Dehydration, altered electrolytes, and hemodynamic instability are a few of the signs and aftereffects of gastrointestinal blockage caused bygallstone ileus and Bouveret syndrome. When selecting the best intervention for each unique patient, these problems must be addressed and managed (Zaliekas and Munson, 2008).

6. Diagnostic approach

By using history collection, physical examination, blood testing, ultrasound, and other imaging techniques, cholelithiasis can be diagnosed.

6.1 Laboratory tests

A number of laboratory tests should be taken into account when determining the cause of cholelithiasis. A normal white blood cell count (WBC) test may not always rule out the possibility of making the diagnosis. Other laboratory tests include the stool guaiac test to rule out intestinal bleeding in cases when the signs of occult or extensive gastrointestinal bleeding are present, the liver function test, lipase, amylase, urinalysis, pregnancy test in women of reproductive age, and pregnancy testing (Febyan and Ruswhandi, 2020).

6.2 Imaging tests

To guarantee early management and avoid complications, cholelithiasis requires an accurate imaging modality. Ultrasonography (USG), computed tomography (CT), and magnetic resonance cholangiopancreatography (MRCP) are among the most effective diagnostic techniques. Patients with gallstones are typically diagnosed via abdominal X-rays and ultrasonography (US). For cases that are unclear, endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS), intraductal ultrasound (IDUS), and magnetic resonance cholangiopancreatography (MRCP) should be performed. These tests should also be used to diagnose any complications, such as cholecystitis, cholangitis, liver abscesses, and biliary cancers (Tazuma *et al*., 2019).

Only 15-20% of gallstones are radio-opaque on X-rays, making the diagnosis of gallstones by plain radiography difficult (Murphy *et al*., 2020). The most accurate way to diagnose gallstone disease is via right upper quadrant ultrasonography. It has a greater than 95% sensitivity and specificity for the detection of gallbladder stones (>15 mm in diameter) and is a non-invasive, safe, widely available, and affordable treatment. Abdominal radiography or CT plays a supporting role to ultrasonography as the primary method for gallstone detection (Portincasa *et al*., 2006).

For the diagnosis of gallbladder stones, computed tomography (CT) is less helpful. It can precisely depict gallbladder distention and wall thickening and spot acute cholecystitis consequences such as perforation, abscess growth, and gallbladder wall emphysema. In emergency hospital settings, it is frequently utilized before surgery (EASL, 2016). However, extra-biliary gallstone pathology and consequences from cholecystitis and pancreatitis caused by gallstones can both be effectively assessed with CT (Murphy *et al*., 2020). Since only 10% of gallstones are calcified and therefore identifiable as radiopaque entities in the right upper quadrant, abdominal radiography and computed tomography are rarely helpful (Portincasa and Moschetta, 2006).

For the visualization and removal of the impacted stones, endoscopic retrograde cholangiopancreatography (ERCP) offers both diagnostic and therapeutic significance. For the diagnosis of choledocholithiasis, magnetic resonance cholangiopancreatography (MRCP) has been employed. Similar to ERCP, MRCP is accurate. When choledocholithiasis is suspected in patients undergoing laparoscopic cholecystectomy for gallstones, MRCP may be useful for preoperative screening. In this case, some surgeons favor ERCP and laparoscopic cholecystectomy (Portincasa *et al*., 2006).

7. Treatment

Conventional surgical, radiologic, and pharmacological therapy can handle the majority of patients with symptomatic cholelithiasis (Gaglio *et al*., 1996).

7.1 Non-surgical care

Treatment for gallstones includes endoscopic, percutaneous catheter, oral, and external shock-wave lithotripsy (ESWL) methods.

- **Analgesia:** Diclofenac plus an opioid (such as morphine or pethidine) are both highly effective for treating acute attacks. The symptoms are frequently accompanied by vomiting; hence, a suppository or injection is advised.

- **Percutaneous drainage:** In patients who are at high surgical risk, percutaneous cholecystostomy enables the resolution of sepsis. 98% of patients who underwent percutaneous transhepatic cholecystostomy for 55 patients had effective biliary drainage; 95% of them made a full recovery and were discharged from the hospital (Sanders and Kingsnorth, 2007). With a median follow-up of 14 months, the surgery played a significant role in the management of elderly and high-risk patients (Qu *et al*., 2019).
- **Drug dissolution therapy:** For patients who reject surgery or pose a poor risk, oral bile salts have been used to dissolve gallstones and these attempts were began from more than 30 years ago. Both chenodeoxycholic acid (chenodiol) and ursodeoxycholic acid (ursodiol) are known to dissolve gallstones over 6 months to 2 years period; chenodiol is more likely to result in diarrhoea and elevated aminotransferase levels, whereas ursodiol does not cause diarrhea. Only a small percentage of patients with symptomatic cholesterol gallstones are candidates for bile salt therapy. Patients who require immediate treatment for acute cholecystitis or common bile duct stones should not use it. Following the cessation of oral bile salts, gallstones frequently recur (Njeze, 2013).
- **Extracorporeal shockwave lithotripsy (ESWL):** The emerging nonsurgical treatments for gallstone disease, such as ESWL, rely on fragmentation. By using endoscopic or transhepatic instruments, ESWL or direct delivery of energy can result in fragmentation. The latter includes mechanical (basket) and laser lithotripsy, for instance. The stones are broken into tiny bits by focusing ultrasonic shock waves upon them in this manner. They are then successfully eliminated in the feces. However, this method of treatment is only appropriate when there are few gallstones present (Way, 1989).

7.2 Surgical care

A cholecystectomy (removal of the gallbladder) has a 99% likelihood of preventing cholelithiasis from returning. Surgery is only recommended for those who are symptomatic. Cholecystectomy is a surgical procedure that has two options.

- **Open cholecystectomy:** This procedure involves making a laparoscopic abdominal incision just below the lower right ribs. 3 to 5 days hospital stay are usually needed for recovery, followed by a week of returning to a regular diet and several weeks of returning to regular activities (Sharma *et al*., 2019).
- **Laparoscopic cholecystectomy:** For the majority of individuals with symptomatic gallstones, laparoscopic cholecystectomy is advised. Expectant management, however, is a respectable substitute as well. The most common abdominal surgery in developed nations is laparoscopic cholecystectomy, with almost 900,000 procedures carried out each year in Europe and the United States (Abraham *et al*., 2014). In comparison to open cholecystectomy, laparoscopic cholecystectomy performed by skilled surgeons, has a number of benefits, including a shorter hospital stay, less postoperative pain, a speedier return to full activity, and a better cosmetic outcome. Many surgeons think that all patients who need cholecystectomy should have the procedure using this technique as the first step. Complications, such as laceration of the right hepatic duct or common bile duct, have increased as this procedure has become more widely used (Aucott *et al*., 1993). With little foetal and maternal morbidity, laparoscopic therapy of symptomatic cholelithiasis during pregnancy is possible (Affleck *et al*., 1999). Cholelithiasis is more common in people with cirrhosis; however, laparoscopic cholecystectomy is safe for people with early cirrhosis (Khan *et al*., 2016). It provides the greatest surgical care with fewer problems (Pimpale *et al*., 2019).

7.2.1 Postoperative complications

The risks associated with cholecystectomy include postoperative complications. Gall bladder bed hemorrhage, infection (typically of the hemorrhage), bile leak, unintentional injury (to the intestine or bile duct), and retained stone in the bile duct are all complications. The most severe is bile duct injury, which happens in both laparoscopic and open surgery with an incidence of 0.2%. The bile duct may require additional surgery to be repaired (Sanders and Kingsnorth, 2007). Discarded gallstones are the most frequent side effects of laparoscopic cholecystectomy and include gallbladder perforation, bile spilling, and gallstones. Stone spillage is more likely when there is cholecystitis, the patient is older, has pigmented stones, there are more than 15 stones, and residents are involved. Even though most lost stones are silent, they might nonetheless result in cutaneous sinus formation, abscess formation, or wound infection. While it is not a significant problem during open cholecystectomy, controlling bile and stone leakage might be difficult during laparoscopic surgery. According to estimates from Luu and Deziel (2014), problems follow laparoscopic cholecystectomy in 2% of instances where missing stones are present (Luu and Deziel, 2014).

It is generally accepted that cholecystectomy is not recommended for individuals with asymptomatic stones because the procedure may be associated with short or long-term consequences. Effective cholecystectomy prevents the majority of gallstone-related complications (Halldestam *et al*., 2004). Given the low rate of problems seen and the good natural history documented in adults, we advise expectant care with periodic clinical and ultrasonographic controls for gallstones that are asymptomatic (Corte *et al*., 2008).

7.3 Herbal treatment

Allopathic drugs and other treatments were also used to dissolve gallstones, but herbal remedies acted as a prophylactic as well as a treatment. Some herbs are used for culinary purposes and are consumable. Herbals are cheap, safe, and have fewer side effects than allopathic drugs (Sri Bharathi *et al*., 2021;Vijayalakshmi *et al*., 2022; Vivekanandan *et al*., 2018). The review highlights the plants and dietary herbals used to treat gallstones. The majority of them were found to be members of the *Fabaceae* family, including *Erythrina lysistemon, Macrotyloma uniflorum, Cyamopsis tetragonoloba (*Lalitha *et al*., 2022), and *Trigonella foenum-graecum*, which have all been tested in various animal models for their ability to prevent gallstones. It also includes other herbal plants from the *Amaryllidaceae, Caryophyllaceae, Lamiaceae, Polygonaceae*, and *Zygophyllaceae* families.The research on the preventative benefits of herbal plants on gallstones is compiled in Table 1 and Figure 2. The botanical names, family names, parts used, dose, methods, and evaluation have also been tabulated.

Table 1: Plants used in cholesterol gallstones (cholelithiasis)

Plant used	Part used	Extract type	Dose	Animal used	Method	Parameters	Evaluation	Reference
Erythrina lysistemon Fabaceae	Stem Bark	AIF and AME from ethyl acetate extract	0.1, 1 and 10 mg/kg	Juvenile female Wistar rats	Ovariectomized rats treated s.c for 3 days	Liver collected and mRNA of gene of interest analysed by real-time PCR.	They upregulate the mechanisms promoting HDL-cholesterol and bile acid formation. It prevents cholesterol gallstone formation.	(Mvondo *et al*., 2014)
Fagopyrum esculentum Moench (buck wheat) Polygonaceae	Seeds	BWP; PBF	BWP (30.7) PBF (54%)	Male mice	Fed with chol esterol enriched diets along with BWP and PBF for 27 days.	Gallbladder was immediately removed and analysis done.	Dietary PBF and BWP significantly decreased the incidence of chol-esterol gallstones and lithogenic index in mice	(Tomotake *et al*., 2006)
Fagopyrum esculentum	Seeds	BWP	525 g/kg (BWP)	Male Golden Syrian hamster	Fed with 5g/kg cholesterol diet along with BWP for 2 weeks.	Blood samples, bile and Feces was collected and plasma, liver lipids, biliary lipid, fecal steroid were analysed.	BWP suppresses gallstone formation and cholesterol level by enhancing bile acid synthesis and fecal excretion of both neutral and acidic steroids.	(Tomotake *et al*., 2000).
Allium sativum and *Allium cepa* Amarylli-daceae	Bulb	Powder	Garlic (0.6%) Onion (2 %)	Male albino mice	LG diet along with onion and garlic (rawor heat processed) for 10 weeks.	Body weights recorded at weekly intervals. Gall-bladders collected and volume of bile, weight of gallbladder with stones was measured and graded.	Dietary Allium spices exerted antilithogenic effect by decreasing the cholesterol hyper -secretion into bile and increasing the bile acid output.	(Vidyashankar *et al*., 2009)
Glechoma hederacea extract (Hitrechol) Lamiaceae	Plant	Hitrechol capsule in aqueous solution.	2.4 ml/kg	Male C57BL/6 mice	LG diet along with Hitrechol for 3 weeks	The bile com-position, anti-inflammatory and anti-oxidative biomarkers detected.	It decreased the size and amount of gallstone crystals, total cholesterol level, total bile acid, inflammatory and oxidative stress markers.	(Xiao *et al*., 2021)
Guatteria gaumeri Annonaceae	Bark	Infusion	0.24 ml	Male golden hamster	Lithogenic diet (80% butter-fat) for 8 weeks. Then infusion was given every 12 h for another 21 days.	The weight of stones calculated. Gallstones observed under SEM (scanning electron micro-scope) and light microscopic.	A corrosive action over the calculi surfaces and galls-tone dissolution effect is seen.	(Betancourt *et al*., 1987)
Herniaria-hirsuta Caryophyl-laceae	Aerial parts	Herbal extract	48.5 mg/kg	Dog	Given 200 g horse meat + 50 % fat (sheep) for 120days, then fed only 200 g horse meat till day 180. Treatment started from 30 th day.	Blood and bile sample collected every 30 days, concentration of cholesterol was determined.	On prolonged use it causes cholesterol -lowering effect in the bile which prevents the forma-tion of gallstones.	(Dooren *et al*., 2015)

Juniperus communis Cuperssaceae	Leaves	Methanolic extract	150, 300, 450 mg/kg	Wistar Albino Mice	Dietcontaining cholesterol (1%) for 6 weeks along with test substance.	Histopathological studies done. Cholesterol gall stone was evaluated under microscope and gallstone scoring done. Plasma cholesterol was analysed.	It reduced the biliary cholesterol levels, plasma cholesetrol and the gallstone incidence reduced by 15–39%.	(Bais and Patel, 2020)
Larrea tridentata Zygophyl-laceae	Leaves and twigs	Ethanolic and aqueous extract.	0.5% EE 1% AE	Male golden hamster	Lithogenic diet for 62 days along with EE and AE.	Bile volume noted gravimetrically. Gallbladder examined for gallstones.	EE prevents chole-sterol gallstone formation and lowered the biliary cholesterol.	(Arteagam *et al*., 2005)
Lysimachia-christinae Primulaceae	Whole plant	*Lysimachia Aqueous* Extract	370 mg/ml, 556 mg/ml, 830 mg/ml.	Male C57BL/6J mice	Lithogenic diet for 8 weeks along with test treatment-orally once a day.	Histopathological studies done. Gallbladder examined for gall-stones and body weight noted.	Gallstone formation was reduced greatly after LAE treatment. Body weight gain and hyperlipidemia is also reduced.	(Liu *et al*., 2021)
Macrotyloma uniflorum Fabaceae	Seed	Methanolic and Acetone extract (AE)	150, 300 mg /kg of both ME and AE	Wistar albino mice	Lithogenic diet for 8 weeks followed by ME and AE for 6 weeks.	Gallbladder was collected and weighed. Bile was analyzed and gallstones scored.	AE decreased the gallstone incidence by 60.21%, and serum total cholesterol. AE has the maximum effect.	(Bigoniya *et a*l., 2014)
Raphanus sativus (black radish) Brassicaceae	Tubers	Juice - black radish root	0.1 ml of juice.	Adult female Mice	LG diet for 34 days then treated for 6 days with JBR juice dilu-ted (1:100), (1:10) and juice concentrate.	Histopathology of liver and gall-bladder done. Cholesterol, HDL cholesterol and triglycerides levels measured.	The juice reduced the incidence of gallstone confirmed by histopathological evaluation. It reduced the cholesterol and triglycerides level.	(Torres *et al*., 2012)
Cyamopsis tetragonoloba Fabaceae	Tender cluster beans	Powder	10%bean powder or 1% of garlic or both	Wistar albino rats	Lithogenic diet along with test for duration of 6 weeks.	Evaluating the biliary glycopro-teins, LMW, HMW proteins and cholesterol crystal growth in bile.	CB reduced the cholesterol content of the bile and biliary protein content, increased bile secretions and prolonged the cholesterol nucleation time.	(Raghavendra and Srinivasan, 2015)
Trigonella foenum-graecum (fenugreek) *and Allium cepa* (onion). Fabaceae	Seeds and bulb	Powder	Powder of fenugreek (12%), Onion powder (2%) and both.	Male albino mice	Lithogenic diet with high cholesterol (0.5%) along with testfor 10 weeks.	Weight of stones and gallbladder was measured. The stones eval-uated and graded. Volume of bile, Cholesterol levels, and Antioxidant levels measured.	Fenugreek, onion and their combi-nation lowered the incidence of choles-terol gallstones by 75%, 27% and 76%, respectively.,	(Reddy and Srinivasan, 2011)
Trigonella foenum-graecum Fabaceae	Seed	Powder	5%, 10% and 15% (w/w).	Male albino mice	LG diet with 0.5% cholesterol with test for 10 weeks. It is also studied in pre-established gall-stones using 6% and 12% w/w powder for 10 weeks.	Bile volume, weight of gall-bladder with stones recorded. CGS evaluated by magnifying lens.	Dietary fenugreek reduced the gallstone incidence by 63%, 40% and 10% in 3 test groups.	(Reddy and Srinivasan, 2009)

Apium graveolens (Celery) Apiaceae	Whole celery plant	Ethanolic extract	1 % w/v	-	Gallstones obtained from a female sickle cell patient and evaluated *in vitro* by stirring 3 separate weighed gallstones over 72 hours.	Stone dissolving capacity measured by average weight of stone.	The ethanol celery extract treatment reduced the weight of gallstone.	(Ajala, and Fajolu, 2020)
Citrus limon Rutaceae	Fruits	Lemon juice	130 mL	-	In in-vitro the stones of different weights were placed in investigated liquid mediaat 20 ℃ The samples were subjected to stirring at 400 rpm.	The weight reduction (WR) of stones, as well as pH of solutions was measured every 24 hours till 7 days.	LJ was found to reduce the weight of stone by 26%.	(Chekroune and Benamara, 2017).
Malva sylvestris L. Malvaceae	Leaves	Infusion	30 ml	-	The dissolving power of the sylvestan mallow towards cholesterol-like gallstones was evaluated over a period of 8 weeks *in vitro*.	Gallstone weight reduction after treatment with infusion was measured	Dissolution was significant with an average mass loss of 31.7 mg and 21.49 mg respectively for the low and medium weight gallstones.	(Amoura *et al*., 2018)
Prunus armeniaca L. (apricot) Rosaceae	Apricot Fruit and Kernel	Extract	1 mg/ml and 2 mg/ml	-	Human gallstones (cholesterol and pigment stones), incubated in human bile and treated by *in vitro* with a combination of apricot fruit and kernel extracts in two doses (1mg/ml and 2 mg/ml) for 4 weeks.	Dried weight of gallstones and the amount of cholesterol released, before and after treatment were calculated.	The dried weight of gallstones was reduced and the amount of cholesterol released from gallstones was increased in a dose-dependent manner.	(Tiwari and Sah, 2020)

(LG: Lithogenic, AIF: Alpinum isoflavone, AME: abyssinone V-4'-methylether, S.C: subcutaneous, BWP: buckwheat protein extract, PBF: high protein buckwheat flour, EE: Ethanolic aqueous extract, AE: aqueous extract, ME: Methanolic extract, LAE: *Lysimachia* Aqueous Extract, JBR: Juice - black radish root, CB: Tender cluster beans, LMW: Low molecular weight, HMW: High molecular weight, LJ: Lemon juice).

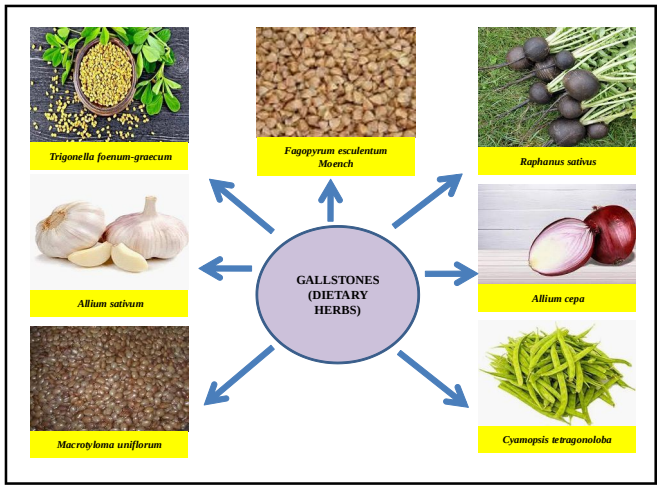

Figure 2: Dietary herbs used to treat gallstones.

7.3.1 Herbals acting on gallstones

Different types of plants have activity against gallstones like *Apium graveolens, Bauhinia cumanensis,Citrus limon, Eleusine indica, Ficus carica, Gomphrena globosa, Kalanchoe pinnata, Musa paradisiaca Solanum melongena*, *Tribulus terrestris*, and *Zea mays*. However, for testing the scientific validity of these herbal preparations clinical studies are required, to establish their safe therapeutic use (Alok *et al.*, 2013). Table 2 shows the list of plants traditionally having gallstone dissolving property yet there is no study carried using these plants in animal models.

Table 2: List of medicinal plants traditionally used in gallstones (Ahmed, 2020)

Botanicals name	Common name	Part/Mode of preparation
Achillea millefolium (Asteraceae)	Yarrow	Leaves decoction
Aloe barbadensis (Liliaceae)	Aloe vera	Leaves juice
Bauhinia cumanensis Kunth. (Fabaceae)	Monkey step/ladder	Whole plant
Berberis aristata.(Berberidaceae)	Citra	Roots
Brassica napus (L.) (Brassicaceae)	Argentine canola	Seed oil
Caulophyllumrobustum Maxim.(Berberidaceae)	Papoose root	Roots decoction
Chamaesycehirta (L.) (Euphorbiaceae)	Asthma plant	Whole plant
Citrus sinensis (L.) (Rutaceae)	Sweet orange	Fruit juice
Curcuma longa (L.) (Zingiberaceae)	Turmeric	Roots
Eutrochium purpureum (L.) (Asteraceae)	Joe pye weed	Roots decoction
Hydrangea arborescens (L.) (hydrangeaceae)	Smooth hydrangea	Roots
Matricaria chamomilla (L.) (Asteraceae)	Chamomile	Flowers decoction
Musa spp. (Musaceae)	Banana	Pseudostem juice
Phyllanthus amarus (Phyllanthaceae)	Indian gooseberry	Leaves
Rhamnus purshiana (Rhamnaceae)	Buckthorn	Bark
Tamarind indica (Fabaceae)	Tamarind	Fruits
Trianthemamonogyna (L.) (Aizoaceae)	Black pigweed	Leaves
Tribulus terrestris (L.) (Zygophyllaceae)	Gokshur	Leaves
Vaccinium macrocarpon (Ericaceae)	American cranberry	Berry juice
Zea mays (L.) (Poaceae)	Corn	Cobs and corn silk
Zingiber officinale (Zingiberaceae)	Ginger	Rhizome

7.3.2. Herbal derivatives reported in animal models

- **Ascorbic acid**

Decreased cholesterol activity of the rate-limiting enzyme 7-hydroxylase causes a rise in the concentration of biliary cholesterol and bile supersaturation. The production of gallstones requires the supersaturation of bile with cholesterol. Ascorbic acid levels in the liver have an impact on cholesterol catabolism in guinea pigs; hypovitaminosis C decreases cholesterol 7-hydroxylase activity. Ascorbic acid-deficient guinea pigs usually develop cholesterol gallstones (Simon, 1993).

- **Curcumin and Capsaicin**

Male mice were used to test the effectiveness of capsaicin and curcumin in reversing pre-existing CGS (cholesterol gallstones). After the stone development in rats, a 0.5% curcumin or a 5 mg% capsaicin diet was given for 5 or 10 weeks, respectively. Later curcumin/ capsaicin diets resulted in a regression of CGS in 45-64% and 80% of the animals, respectively. With increased duration of the feeding of test compound, biliary cholesterol reduced while phospholipids and bile acids increased (Hussain and Chandrasekhar, 1994).

- **Curcumin and piperine**

Gallstone development might be avoided by curcumin. It has a low bioavailability due to limited absorption and faster metabolic changes. So, when piperine, a bioavailability enhancer, is added to it, the bioavailability of curcumin can be increased, improving curcumin's efficacy. For 4 weeks, curcumin and piperine were added to a lithogenic diet that was given to C57BL6 mice. Combining curcumin with piperine can significantly increase its effects, prevent the formation of gallbladder stones, lower the lipid and bile saturation, and reduce the expression of NPC1L1 and SREBP2 (which may be contributing to the formation of gallstones) at the protein levels and m RNA (Li *et al.*, 2015).

- **Melatonin**

Gallstone formation has been linked to oxidative stress caused by free radicals. Melatonin (MLT), a free radical scavenger, guards against the development of pigment gallstones. In a guinea pig model, a

study was conducted to look at the changes in oxidative stress that occur during the production of pigment gallstones and to see if melatonin (MLT) may be used as a chemopreventive drug for cholelithiasis. Guinea pigshad their common bile ducts tied off with or without MLT pretreatment and the results were examined after 14 days. Without MLT, stones are formed in the ligated guinea pigs. In order to assess the effects of oxidative stress on lipoperoxides and total antioxidant activity in bile and serum, various parameters were studied. MLT returned the MDA (Malondialdehyde), pH, TAA (total antioxidant activity), and biliary bile salts to their pre-ligation states. It demonstrated a connection between the development of pigmented gallstones and oxidative stress in guinea pigs after bile duct ligation. The increased oxidative stress was restored by antioxidant therapy with MLT, and gallstone development was likewise avoided (Shiesh *et al*., 2000).

· **Piperine**

In order to control the biliary cholesterol that contributes to cholesterol gallstones, piperine (PA), a possible cholesterol-lowering medication, was utilized. In a study, mice were fed high-cholesterol diets with or without PA (at 15, 30, or 60 mg/kg) for 10 weeks, to see if cholesterol gallstones would form. Pathological alterations, the expression of proteins in the liver, bile phospholipids and crystals, serum lipids, and cholesterol were all examined. It revealed that PA could lower total cholesterol (TC), TG, and enhance serum HDL levels in addition to lowering the potency of cholesterol and bile stones. By reducing MDA and raising SOD (Superoxide dismutase), PA therapy decreased liver lipidperoxidation and shielded the hepatobiliary cells from liver damage. Additionally, it decreased the transport of cholesterol from the hepatocytes to the gallbladder and suppressed the expression of the liver's ATP-binding cassette transporters G5/8 and liver X receptor (LXR). It might be how PA prevents cholesterol gallstones from forming. According to Song *et al*., (2015), PA may be used as a medication to prevent cholesterol gallstones.

7.3.3 Chinese herbal treatment

Traditional Chinese Medicine (TCM) has a long history of thousands of years of clinical practice in China and has become more and more significant in the preservation of health and the treatment of disease. TCM is viewed as a promising alternative medicine approach for treating complicated disorders globally (Huang *et al*., 2019). Chinese medicinal plants are typically characterized as a collection of therapeutic plants that work well together (Gan *et al*., 2013). Various TCM treatments for gallstones have been studied, including Lidan Granule in guinea pigs (Wu *et al*., 2016), Qingre Lidan Decoction (QRLDD) (a classic 6-herb pre-compounded prescription), Yinchenhao Decoction in Mice (Meng *et al*., 2018), and schaftoside in the C57BL/6 mouse model (Liua *et al*., 2017). One of the traditional medicinal practices used in China is Tibetan medicine. According to the Tibetan medical system, cholecystitis can be treated with 170 different types of Tibetan medication and 38 different types of Tibetan prescriptions (Pan *et al*., 2021).

8. Conclusion

Gallstones can form in the hepatic bile duct, common bile duct, or gallbladder as a result of cholelithiasis, a chronic, recurring hepatobiliary illness whose cause is poor cholesterol, bilirubin, and bile acid metabolism. The cholecystectomy procedures are expensive, raise the risk of morbidity and mortality, and cause the illness to recur. Therefore, the patient needs additional therapy choices, such as herbal therapies, for the proper management and prevention of gallstone disease. The negative side effects of conventional medicine have already drawn people's attention to herbal remedies. Due to their safety, effectiveness, cultural acceptance, and lack of adverse effects, medicinal herbs have been utilized for ages to treat stone disease. In contrast to standard treatment methods, this article discusses plants and other alternative cures for diseases that have less side effects. Because health care systems are going to become more and more expensive, we must implement a system of herbal medicine. We anticipatethat, in the future, herbal medicines will be a competitive contemporary treatment with additional added benefits like safety and lowcost because there is currently no concrete evidence of their effectiveness.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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