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# *Kalanchoe pinnatum* in Treatment of Gallstones: An Ethnopharmacological Review

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**Abstract:** Gall bladder is an important organ under the biliary system and there are several diseases which affect this system .Cholelithiasis (gall stones) is one among those conditions which affect the gall bladder .The present article is a review on the basis of the formation of gall stones, its treatment, ethnobotany and ethnopharmacology of *Kalanchoe pinnata* which is claimed to be useful against Cholelithiasis .An attempt is also made to highlight other therapeutic uses of the plant**.** The reported pharmacological properties of *Kalanchoe pinnata* are antitumor, antibacterial, anti oxidant, antileishmanial, hepatoprotective, antimicrobial, antidiabetic, wound healing ,antiulcer ,antidepressant and creatine kinase activity .
**Keywords:** Gall bladder, Cholelithiasis, *Kalanchoe pinnatum.*

## INTRODUCTION

Gallbladder is a small sac located on the right-hand side of the body, just below the liver which is a hollow organ that concentrates and stores bile. It lies in the gallbladder fossa on the inferior aspect of the right lobe. It has a rounded fundus, a body, and an infundibulum. Bile juice which is also called gall is a greenish-brown liquid produced by the liver. Gall goes into the small intestine via the bile ducts to facilitate the digestion, mainly of fats[1, 2]. There are several diseases which arise in the gall bladder and one among them is gall stones (cholelithiasis). The prevalence of gall stone disease is more common in the Western society[3]. In India it shows epidemiological Variations—while it is common in UK, USA and Europe but rare in Africa, China and Japan. Epidemiological study revealed that gall stone disease is more common in women in the north, north-east and east as compared to other zones in the country. Gall stone disease was at least 7 times more common in women in north India as compared to those in south India. Most gall stones (>80%) in north India are cholesterol Stones[4,5] while more than 60% of gall stones in south India are pigment stones and only less than 5% are cholesterol stones.[6]The treatments for choloelithiasis include pharmacotherapy and surgery of which the latter one passes risk to the patients. Even though there exists drug therapy they are rarely used because of their adverse effects and recurrence of gall stones. Hence the present review is made on the folklore and herbal remedies for such ailments. Medicinal plants and their formulations are used enormously for treating a range of illness in ethnic medical practices as well as in the traditional system of medicine in India[7]. Herbal medicines and medicinal plants are not only meeting treatment needs in developing countries but also getting popular in

developed world[8]. The Indian Traditional Medicine like Ayurveda, Siddha and Unani are predominantly based on the use of plant materials[9]**.** Complementary Alternative Medicine is also becoming more and more popular in many developed countries. Forty-two percent of the population in the US have used Complementary Alternative Medicine at least once (WHO 1998), and a national survey reported the use of alternative therapies increased from 34% in 1990 to 42% in 1997 (UNCCD 2000).The WHO has listed more than 20,000 medicinal plants globally in which contribution of India is 15-20%[10]. Also the WHO reported that 80% of global countries depend on the medicinal plants[11].

One of the important and well documented uses of plant products is their use as gall bladder protective agent. Different plants used in the treatment of gallstones are *Apium graveolens, Bauhinia cumanensis, Bauhinia excise, Costus scaber, Chamaesyce hirta, Cissus verticillata, Capraria biflora, Cocos nucifera, Eleusine indica, Ficus carica, Gomphrena globosa,* ***Kalanchoe pinnata****, Portulaca oleraceae, Solanum melongena* etc. [12]. Hence it is high time in the present scenario to understand the importance of utility of medicinal plants and also to appreciate the role of floral wealth in maintaining the state of well being. In this regard the present article reviews the therapeutic activity of a rare plant *Kalanchoe pinnata* which is claimed to be a gall bladder protective agent used in the treatment of Cholelithiasis [13]**.**

## ANATOMY AND FUNCTIONS OF THE GALL BLADDER

The gall bladder is a pear shaped organ, 9cm in length and has a capacity of approximately 50 ml. It consists of the fundus, body and neck that tapers into the cystic duct .The main function of the gall bladder is to store and concentrate the bile secreted by the liver and then deliver it into the intestine for digestion and absorption of fat. The motility, concentration and relaxation of the gall bladder are under the influence of a peptide hormone, cholecystokinin, released from neuroendocrine cells of the duodenum and jejunum[14] .This bile containing high level of cholesterol gets concentrated, becomes hardened, crystalline and doesn't move to the intestine, that is then termed as gall stones[15].Gall bladder stones are mainly cholesterol stones, while pigment stones and mixed stones composed of bile pigments and bile salts are also seen.

## FORMATION AND TYPES OF GALL STONES

Impaired motility of the gallbladder has been cited as contributing factor in the development of gall stones[16]. The gallbladder not only concentrates bile, but also acidifies it. Failure of acidification may promote the calcification of gallstones[17.] One practitioner stated as early as in 1941 that food allergy is a common cause of gallbladder disease, and that failure to recognize food allergy has resulted in many unnecessary cholecystectomies[18.]Gall stones are of three major types- (i) Pure cholesterol stones contain at least 90% cholesterol,(ii) pigment stones either brown or black contain at least 90% bilirubin and (iii) mixed composition stones contain varying proportions of cholesterol, bilirubin and other substances such as calcium carbonate, calcium phosphate and calcium palmitate[19]. Brown pigment stones bilirubin, calcium and tribasic phosphate [20] .In Western societies more than 70 % of gallstones are composed primarily of cholesterol, either pure or mixed with pigment, mucoglycoprotein and calcium carbonate [21]. The pathogenesis of all these three types of gallstones is mentioned below. The pathogenesis of cholesterol gallstones must be briefly considered to facilitate the presentation of epidemiological risk factors such as age, gender[22] diet[23] obesity[24] decreased physical activity[25] rapid weight loss[26] and oral contraceptives[27].These epidemiological risk factors along with reduced bile salt excretion due to cholesterol lowering drugs, or illeal resection leads to nucleation (appearance of crystals)[28,29]. The additional factors for nucleation are reduced antinucleating factors and gallbladder hypomotility[30]. These two factors along with mucin may lead to the aggregation of crystals and hence to the formation of gallstones[31] .In case of pigment gallstone excess bile pigment production due to haemolytic anemias may lead to pigment precipitation which in addition to mucin leads to aggregation and gallstone formation[32]. The biliary calcium concentration helps in bilirubin precipitation and gallstone calcification[33, 34.] Patients with gallstones have increased biliary calcium, with super saturation of calcium carbonate[35.] The calcification of gallstones is also due to the failure of acidification[36.]

## CAUSES AND SYMPTOMS

Pain on the right-hand side of the body just below the ribs, Back pain, Pain in the right shoulder, Nausea, Vomiting and Sweating.

**Infection** - If there is gallbladder infection the patient may have fever and experience shivering.

**Jaundice** - If the gallstone leaves the gallbladder and gets stuck in the bile duct it may block the passage of bile into the intestine. The bile will then seep into the bloodstream and the patient will show signs of jaundice.

**Pancreatitis** - If a small gallstone passes through the bile duct and blocks the pancreatic duct, or causes a reflux of liquids and bile into the duct, the patient may develop pancreatitis[37].

**Biliary colic** - Sometimes the gallstones may pass down through the bile duct into the duodenum. When this happens the patient may experience biliary colic[38].

**Weight loss-** may reduce the risk of gallstone formation in overweight individuals, but excessively rapid weight loss (i.e., more than three pounds per week) may lead to the development of gallstones. The increased risk associated with rapid weight loss is due to an increase in the ratio of cholesterol to bile salts in the gallbladder and to bile stasis resulting from a decrease in gallbladder contractions[39].

**Use of oral contraceptives -**Women taking oral contraceptives and those undergoing high-dose estrogen therapies also one among the causes. Hormone replacement therapy (HRT) for women during the menopause is linked to a higher risk of gallbladder problem[40].

## TREATMENT

### SURGICAL TREATMENT

Laparoscopic gall bladder surgery (cholecystectomy) removes the gallbladder and gall stones through several small incisions in the abdomen. After surgery, bile flows from the liver through the common bile duct into the small intestine. Because the gallbladder has been removed, the body can no longer store bile juice.

**Risk and Side effects**: Inflammation, scar tissue, injury, or bleeding[41] .Complications of laparoscopy is infrequent (3–6%),but can be significant, and include bile duct injuries and the escape of gallstones into the peritoneum[42,43]. In open gall bladder surgery, the gallbladder is removed through a single, large cut (incision) in the abdomen under anesthesia.

**Side effects** : Injury to the common bile duct, Excessive bleeding, Infection of the surgical wound, Injuries to the liver, intestines, or major abdominal blood vessels, Blood clots or pneumonia related to the longer recovery period after open surgery, Risks of general anesthesia[44,45].

### NONSURGICAL TREATMENT FOR GALLSTONES

Nonsurgical treatment is rarely used, as it can only be used for cholesterol gallstones. If a patient has a serious medical condition that would prevent surgery, a nonsurgical treatment for the gallstones may be attempted. The gallstones, however, usually recur after nonsurgical treatment. The types of nonsurgical gallstone treatment include:

#### Oral Dissolution Therapy

Ursodiol and chenodiol have been used and work best for small cholesterol stones. These drugs can take months or even years to dissolve the gallstones.

#### Contact Dissolution therapy

This is an experimental treatment that involves injecting methyl terbutyl ether directly into the gallbladder. This drug can dissolve gallstones in 1 to 3 days. This treatment, however, can be risky because it is a flammable anesthetic and it can be toxic[46].

### HERBAL TREATMENT

In recent years, there has been growing interest in alternative therapies and the therapeutic use of

natural products, especially those derived from plants. The folk medicines and ecological awareness suggest that 'natural'products are harmless[47]. Since the surgical treatment has many risk factors herbal treatment has come into practice. The wonder plant or divine plant *Kalanchoe pinnata* has high therapeutic value against gall stone disease[48]. It is commonly known as a master herb or a cure for all by a large community of tribal and herbal practitioners of various countries[49].

## PLANT DESCRIPTION

The plant grows all over India in hot and moist areas, especially in Bengal. It is a perennial, succulent, stout, erect herb with tuberous and glabrous stems which are mottled with purple scales. It grows up to 1-1.5 m in height and the stem is hollow four-angled and usually branched. Leaves are opposite, decussate, 3-5 lobed, 10-20 cm long. The lower leaves are simple, whereas the upper ones 3-7 foliate and are long-petioled and are fleshy dark green in color. The leaflets with each notch bearing a dormant bud competent to develop into a healthy plantlet apex obtuse. The leaves are furnished with rooting vegetative buds. The inflorescence is terminal paniculate cyme with orange –red colored and pendulous flowers. Flowers are many bell-like pendulous in shape. Calyx tubular, 2-4 cm; Corolla is reddish to purple, 5 cm, base sparsely ciliate; lobes ovatelanceolate; stamens inserted basally on corolla; nectar scales oblong; follicles included in calyx and corolla tube. The fruit-pod with four septa and numerous, ellipsoid, smooth striate seeds within. The plant flowers in Nov-Mar and fruits in April[50, 51, 52]. It is astringent, sour in taste and has hot potency.This plant is specially noted for developing small plantlets on the outer edged of its leaves, when its leaves are detached[53].

## VERNACULAR NAMES

Vernacular names for *Kalanchoe pinnata* include Cathedral Bells, Air Plant, Life Plant, Miracle Leaf, Goethe Plant and Katakataka.

**Arabic:**Kushnulhayat;**Ahanti:**Egoror,Tamiawu;**Bengali**:Patharkuchi,Koppata;**Bombay:**Ahiravana,Ghayamari, Mahiravana;**Burma:**Yoekiyapinba;**Cutch**:Ahiravana,Ghayamari,Mahiravana; **Hindi:** Zakhmehaiyat;**Indo-China:**Pounpo,Poun tay ,Thuoc binh,Thuocbong;**Krobo:**Kokonadu; **Malayalam:**Elamarunga,Elamarunna.Murikuti;**Mundari:**Jiwan,Sajiwan;**Persian:**Chubehayat,Lakhmhaiyat;**Sanskrit:**Astibhaksha,parnabeeja;**Tamil:**Malaikalli ,Runakalli;**Telugu :**Simajamudu ;**Urdu:**Chubehayat [54].

## TAXONOMY

The genus Kalanchoe belongs to the order Saxifragales and Crassulaceae family (table 1).

**Table 1. Taxonomy of *Kalanchoe pinnata***

| | |
|---|---|
| Kingdom | Plantae |
| Division | Magnoliophyta |
| Class | Magnoliopsida |
| Order | Saxifragales |
| Family | Crassulaceae |
| Genus | Kalanchoe |
| Section | Bryophyllum |
| Species | K. pinnata |

## CHEMICAL CONSTITUENTS

*Kalanchoe pinnatum* was reported to contain alkaloids, triterpenes, glycosides, flavonoids, Cardienolides, steroids, bufadienolides and lipids [55,56,57]. The leaves contain bufadienolides like Bryotoxin A, B, C which are very similar in structure and activity as two other cardiac glycosides, digoxin and digitoxin and possesses antibacterial, antitumor, cancer preventative and insecticidal actions[58,59].The leaves also contain p-coumaric acid, ferulic acid, syringic acid, caffeic acid, isocitric acid, malic acid,p-hydroxy benzoic acid, flavanoids like quercetin, kaempferol, n-henticontane, n Tritiacontane,sitosterol[60]. Bufadienolides- Bryophyllin A, Bryophyllin B, Bryophyllol , Bryophollone, Bryophellenone, Bryophynol[61,62.]

## USES

*Kalanchoe pinnatum* leaves and pods enhance the reducing properties of the calcium oxalate crystals. Similar result have also reported by Fauzia Yasir and Muhammad A. Waqar (2011) that *B. pinnatum* extracts have antiurolithic activity and have the ability to reduce crystal size as well as to promote the formation of calcium oxalate dihydrate (COD) crystal[63]. Leaves are used as astringent, antiseptic, and counterirritant against poisonous insect bites. Fresh plant material is applied as a poultice for a variety of conditions: Sprains, eczema, infections, burns, carbuncle and erysipelas. In Ayurveda, useful in vitiated conditions of vata and pitta, cuts, wounds, hemorrhoids, menorrhagia, boils, sloughing ulcers, burns and scalds, diarrhea, dysentery, headaches, vomiting, bronchitis[64].

## PHARMACOLOGICAL ACTIVITIES OF THE PLANT

*Kalanchoe pinnata* has been reported to have multiple biological effects which are summarized in Table 2 and commented as under.

**Table 2. Summary of Pharmacological activities of *Kalanchoe pinnata***

| **Pharmacological activities** | **References** |
|---|---|
| Anti tumor | Unang Supratman et al.[65] |
| Anti bacterial | Subrata Kumar Biswas et al.[66] |
| Anti oxidant | Manisha Bhatti et al.[67] |
| Anti leishmanial | Michelle F. et al.[68] |
| Hepatoprotective | N.P Yadav and V.K Dixit [69] |
| Anti microbial | Akinsulire OR et al.[70] |
| Anti diabetic | Patil SB et al. [71] |
| Wound healing | Nayak BS et al. [72] |
| Anti ulcer | Adesanwo JK et al.[73] |
| Anti depressant | B.Joseph et al.[74] |
| Creatine kinase | Chibueze Nwose [75] |
| Neurosedative/muscle relaxant | O K Yemitan et al. [76] |

## ANTI TUMOR ACTIVITY

Unang Supratman et al., reported the anti tumor promoting activity of three bufadienolides isolated from *Kalanchoe pinnata* which were examined for their inhibitory effects on Epstein Barr virus induced early antigen activity which included the tumor promoter 12-O-tetradeacanoylphorbol-13 acetate. All bufadienolides exhibited inhibitory activity; Bryophyliin A showed the maximum inhibitory activity. Bryophyllin C, a reduction analogue of Bryophyllin A, and bersaldegenin -3-acetate lacking the orthoacetate moiety were less active .These results suggested that bufadienolides are potential cancer chemo preventive agents[65].

## ANTIBACTERIAL ACTIVITY

Subrata Kumar Biswas et al., reported the presence of alkaloids, glycosides, steroids, gums, flavanoids, saponins, reducing sugars and tannins in the ethanolic extracts of *Kalanchoe pinnata* Linn. The study also reported significant antibacterial activity against gram positive (*B.* Subtilis, S. aureus*)* and gram negative *(*E. coli, P. aeruginosa, S. dysenteriae*)* bacteria with the zones of inhibition ranging from 6.0±0.35 to 8.2±0.22 mm. The results provided a support for the use of this plant in traditional medicine as an antibacterial and could be used as a pesticide[66].

## ANTIOXIDANT ACTIVITY

Benzene, chloroform, acetone and ethanol extracts of leaves and stems of *Kalanchoe pinnata* was Subjected to the evaluation of total phenolic, flavanoid content and in vitro anti oxidant potential. The plant powder (100 mg) yielded 0.49, 0.64, 0.99, 1.17 %w/w total phenolic content in leaves and 0.18, 0.27, 0.48, 0.62 %w/w total phenolic content in the stem in benzene, chloroform, acetone, ethanol extracts respectively using gallic acid as standard .The results of the study indicated that the plant contained 0.24, 0.37, 0.56, 0.75 %w/w of total flavanoids in leaves and 0.15, 0.22, 0.42, 0.54 %w/w of total flavanoids in stem in the benzene, chloroform, acetone, ethanol extracts respectively using quercetin as standard. The extracts showed significant antioxidant activity in dose dependent manner. The result obtained in the study indicated that leaves and stems of *K.* pinnatum as a source of natural antioxidant [67]

## ANTILEISHMANIAL ACTIVITY

Michelle F et al., reported Antileishmanial activity and the presence of various phytoconstituents in *Kalanchoe pinnata*.The study of aqueous leaf extract of the plant revealed the presence of a kaempferol di-glycoside, named kapinnatoside, identified as kaempferol 3-O-α-l-arabinopyranosyl (1 → 2) α-l-rhamnopyranoside, quercetin 3-O-α-l-arabinopyranosyl (1 → 2) α-l-rhamnopyranoside and 8-dimethoxyflavone 7-O-β-d-glucopyranoside.[68]

## HEPATO PROTECTIVE ACTIVITY

Yadav NP and Dixit VK reported hepatoprotective activity of *Kalanchoe pinnata* leaf juice and the ethanolic extract of the marc left after expressing the juice in rats against CCl4-induced hepatotoxicity. The test material was found effective as hepatoprotective as evidenced by liver function tests and in vitro histopathological studies [69].

## ANTI MICROBIAL ACTIVITY

Extracts from the leaves of *Bryophyllum pinnatum* were screened for their antimicrobial activities against some gram-negative organisms (*Escherichia coli* ATCC 25922, *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Shigella flexneri, Salmonella paratyphi*, Citrobacter spp); gram-positive organisms *Staphylococcus aureus ATCC 25213, Staphylococcus aureus, Enterococcus faecalis, Bacillus subtilis*) and a fungus (*Candida albicans).* Agar well diffusion and broth dilution methods were used to determine the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) at concentrations of 512 mg/ml to 4 mg/ml. All the organisms except *Candida albicans* were susceptible to the plantextracts. The gram-positive organisms were more sensitive to the methanol and local gin-extract of Bryophyllum pinnatum[70].

## ANTI DIABETIC ACTIVITY

Patil SB et al., reported anti diabetic activity of dichloromethane (DCM) fraction of *Kalanchoe pinnata* leaves obtained by steam distilling of *Kalanchoe pinnata* leaves followed by solvent fractionation using dichloromethane (DCM) against streptozotocin induced diabetes model. In the in vivo studies, rats were treated with 5 and 10 mg/kg body weight of DCM fraction for 45 days orally. Lipid profile and other biochemical parameters were estimated. The probable mechanism for insulin secretagogue action was evaluated through studies using diazoxide and nifedipine.The bioactive component from DCM fraction was studied using HPTLC, GCMS and IR. Invitro studies demonstrated a dose-dependent insulin secretagogue action. The results revealed insulin secretion to be 3.29-fold higher at 10µg/ml as compared to the positive control. The insulin secretagogue activity was glucose independent and K(+)-ATP channel dependent. The DCM fraction of Kalanchoe pinnata demonstrated excellent insulin secretagogue action [71].

## WOUND HEALING ACTIVITY

The ethanol extract of *Kalanchoe pinnata* was evaluated for its wound healing activity using excision wound model in rats. On day 11 animals treated with the leaf extract exhibited 86.33% reduction in the wound area, compared to petroleum jelly treated control (69.36%) and the mupirocin treated standard (85.49%). Also the histological analysis being significant proved the wound healing potential of the plant. The increased rate of wound contraction and hydroxyproline content in the extract supported the claims made by traditional healers [72].

## ANTI ULCER ACTIVITY

Adesanwo JK et al., reported antiulcer activity of methanolic extract of leaves of *Bryophyllum pinnatum* on ndomethacin induced gastric ulcers in rats. The results showed significant reduction($p<0.05$)in the incidence of ulceration and mean basal and histamine (1 mg kg-') stimulated gastric acid secretion in a dose dependent manner justifying the use of Bryophyllum pinnatum as an anti-ulcer agent in folklore medicine[73].

## ANTI DEPRESSANT ACTIVITY

*Kalanchoe pinnata* showed sedative and central nervous system depressant actions in animal studies.These effects were attributed partially to the leaf extract demonstrating the ability to increase the levels of a neurotransmitter in the brain called GABA[74] .

## CREATINE KINASE ACTIVITY

Chibueze NW demonstrated the effect of ethanol extract of fresh leaves of *Kalanchoe pinnata* on the levels of creatine kinase. The albino rats treated with 200mg/kg and 400mg/kg body weight of the extract for seven days resulted in a slight decrease in physical activities and body weight of all the animals when compared to the control group. Further the study revealed a significant increase in serum creatine kinase level in albino rats treated with the ethanolic extract than in the control group.The increase levels of creatine kinase could encourage the supply of energy needed for muscular contraction[75].

## NEUROSEDATIVE/MUSCLE RELAXANT

A Study in mice investigating the neuropharmacological activities of saline leaf extract of *B.pinnatum* showed a dose-dependent prolongation of onset and duration of pentobarbitone-induced hypnosis. It also delayed onset to convulsion in strychnine- and picrotoxin-induced seizures with minimal protection against picrotoxicin seizures [76].

## CONCLUSION

Present article highlights the recent researches on *Kalanchoe pinnata* . It is a rare herb usually referred to as miracle plant, used to treat various diversified physiological conditions. The plant *Kalanchoe pinnata* has a wide array of pharmacological activities and many isolated compounds of the plant lack study on their pharmacological activities and therefore seems worthwhile significantly to validate the pharmacological properties of *Kalanchoe pinnata* , which will substantiate the use of this plant by tribal people. Now it becomes

endangered plant which needs to be conserved as well as explored for its significant biological properties. *Kalanchoe pinnata* imbibing a tremendous potential, deserve a special attention of the scientific fraternity.

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