Review Article

Ethnomedicinal, Botanical, Chemical and Pharmacological Properties of *Bryophyllum pinnatum*

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Received: 18-12-2023; **Revised:** 25-01-2024; **Accepted:** 04-02-2024; **Published on:** 15-02-2024.

ABSTRACT

Herbal medicine is the use of medicinal plants for prevention and treatment of diseases it ranges from traditional and popular medicines of every country to the use of standardized and titrated herbal extracts. Medicinal plants and their secondary metabolites are progressively used in the treatment of diseases as a complementary medicine. It has been reported that *Bryophyllum pinnatum* extracts possess various biological activities viz antiviral, sedative, antiulcer, immunomodulator, central nervous system depressant, anti-inflammatory, thyroid peroxidase inhibitor, cytotoxic, hepatoprotective, antioxidant, analgesic, anticonvulsant, antimicrobial, inhibition of B cell development, cardiovascular, antihyperglycemic, acetylcholinesterase inhibition. Earlier studies on different species of bryophyllum have reported the isolation of polysaccharides, flavonoids, sterols, ascorbic acid, trace elements, organic acids, hydrocarbons, triterpenoids, phenolic components and bufadenolides. This review presents the botany, chemistry, traditional uses and pharmacological data of genus Kalanchoe.

Keywords: *Bryophyllum pinnatum*, anti-inflammatory, cytotoxic, flavonoids, cardiac glycosides.

1. INTRODUCTION

Scientific Name: *Bryophyllum pinnatum*

Common Name: Air plant, cathedral bells, life plant, miracle leaf, Goethe plant, Tamil: Malaikkalli, Runakkalli

Bryophyllum pinnatum (family- Crassulaceae) is widely used medicinal plant in traditional system with a wide range of biological activities. It is a succulent glabrous herb 1- 2 m high, stems obtusely 4-angled, the older light colored, the younger reddish speckled white, leaves variable, decussate, the lower usually simple or occasionally compound, the upper usually 3-5 or 7-folliolate, long petiole, petiole united by a ridge round the stem. leaflets are oval or narrowly oval with rounded tips, and when more than one leaflet is present the end leaflet is usually significantly bigger than the others, crenate or serrate rich in alkaloids, triterpenes, glycosides, flavonoids, steroids, and lipids[1]. The leaves (5-25 cm long and 2-12.5 cm wide) contain a group of chemicals called bufadienolides which are very active similar in structure and activity as two other cardiac glycosides, digoxin and digitoxin[2]. The leaves are used as astringent, refrigerant, emollient, mucilaginous, haemostatic, vulnerary, depurative, constipating, anodyne, carminative, disinfectant and tonic. They are useful in vitiated conditions pitta and vata, haematemesis, haemorrhoids, menorrhagia, cuts and wounds, discolorations of the skin, boils, sloughing ulcers, ophthalmia, burns, scalds, corn, diarrhoea, dysentery, vomiting[3]. Formaldehyde will induce an inflammatory reaction at the site of injection, and this has been used for studying inflammation quantitatively in the rat foot[4]. Selye first described the effect of injected formaldehyde in the rat foot as an arthritic reaction[5].

Geographical areas where *Bryophyllum pinnatum* plant grows:

This is a native to Madagascar. It also grows in southern Africa. It grows in other parts of the world such as Macaronesia, New Zealand, parts of Asia, Nepal, Thailand, Pakistan, Egypt, Brazil, Polynesia, Galapagos Islands, West Indies, Australia, Hawaii, Melanesia, and Mascarenes.

In India, it grows in the Khasi Hills of Assam, Kashmir, and the Himalayan region. Cultivation of the plant occurs in Karnataka, Andhra, Kerala, and Tamil Nadu.

2. ETHNOMEDICINAL OR TRADITIONAL USES

The juice of bryophyllum is used for the local treatment of periodontal disease, cheilitis, cracking lips in children, bruises, wounds, boils in Brazil[6], insect bites in India and Srilanka[7], ear infection, dysentery in Nigeria[8], fever, abscesses, coughs, skin diseases and cytotoxic activity[9], cholera, urinary diseases, whitlow in Africa and Asia[10], tissue injuries in Taiwan[11], arthritis and gastric ulcers[7]. Crushed leaves are rubbed on or tied to the head to bring relief for headache in Africa[8], rheumatism in Indonesia[12], treatment of pulmonary infection, rheumatoid arthritis, immunomodulatory and gastric ulcers[13] (fig 1).

3. BOTANICAL DESCRIPTION

Family Crassulaceae or orpine family (fig 2), stonecrop family, Synonym: Sedaceae, kalanchoe is a large family of dicotyledons, consisting mainly of succulent herbs, but tending to be miniature shrubs or trees in certain genera and species. Most members of the family are remarkable for their xeromorphic structure, particularly the occurrence of water storage tissue in the leaf and stem.

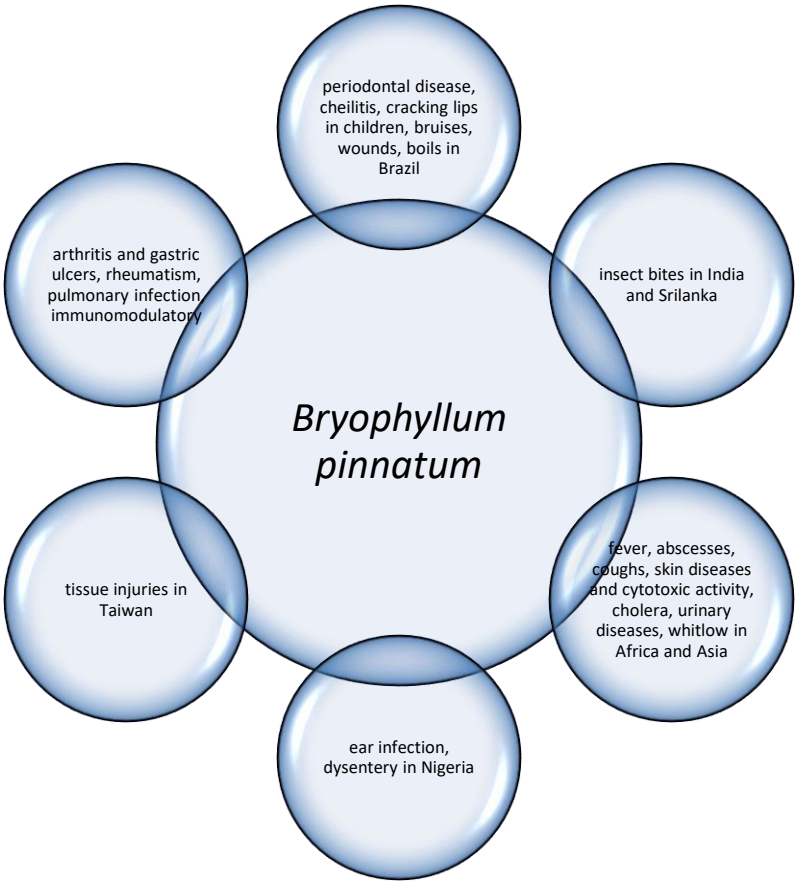


Figure 1: Ethnomedicinal or traditional uses

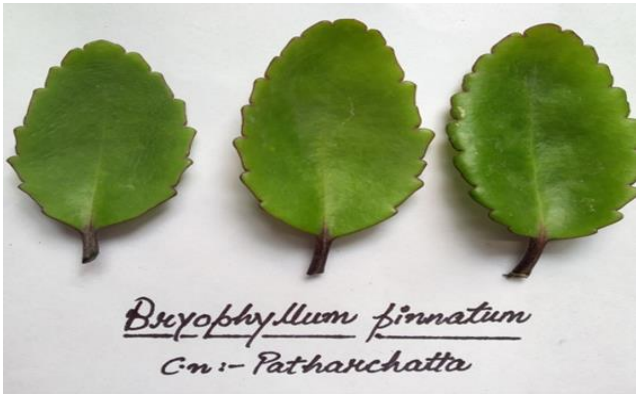


Figure 2: *Bryophyllum pinnatum*

Some are believed to be capable of absorbing water directly from the air by special hairs, epidermal cells or adventitious roots. Members of this family are not considered as important crop plants, but they are used for horticulture; many members have an unusual attractive appearance, and are quite hardy, typically needing only minimal care. Succulent glasshouse herbs or subshrubs, with interesting foliage and flowers. Usually robust erect plants; leaves opposite, fleshy, sessile or stalked, varying from entire to crenate and pinnatifid; flowers yellow, purple or scarlet. Terminal paniculate cymes, rather large and often showy; calyx 4 parted, the narrow lobes shorter than the corolla-tube, usually falling early; corolla 4 parted and mostly spreading, the tube usually cup-shaped; 8 stamens and 4 carpes[14].

The leaf usually centric or intermediate between dorsiventral and centric; typical palisade tissue rare, opposite, or alternate, exstipulate. Stomata are present on all parts of the surface of the leaf; surrounded by a girdle of 3 subsidiary cells. Hydathodes, which appear as small pits or spots on the leaf visible to the naked eye, are variously distributed in different species, sometimes covering the whole of both surfaces, at others confined to one surface or arranged in rows near the leaf margin on both surfaces and only on the lower surface. Secretory cells, with apparently tanniniferous contents, common in undignified tissues, especially around the veins; only rarely morphologically differentiated from neighbouring cells. Crystals common, solitary, clustered, or in the form of sphaerites and crystal sand[14,15].

Microscopical character

1. The microscopic appearance confirms a thin layer on the abaxial side and a convex surface on the adaxial side. It has a thin epidermal layer with small, less prominent cells on the adaxial side. Midrib ground tissue is parenchymatous. Cell are Circular, angular, and compact.

2. The vascular strand is a single, small, hemispherical strand. It is made up of a thick horizontal xylem band and a wide phloem band.

3. Xylem components are narrow, angular, and have thin walls. The vascular bundles are in both the vertical and horizontal planes. The lamina is flat, and the mesophyll is

split into palisade and spongy parenchyma. The stomata are amniocytic in nature and are abundant. 4. Spiral vessels can be seen in the longitudinal section of the leaves. Trichomes are absent on the abaxial and adaxial sides[16].

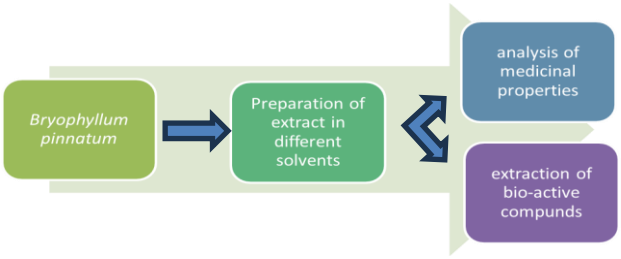


Figure 3: Activity of *Bryophyllum pinnatum*

4. CHEMICAL PHYTOCONSTITUENTS

A number of authors have isolated and identified several compounds from different Bryophyllum species. These compounds may be classified into several groups namely: flavonoid glycosides, anthocyanins, coumarins, bufadienlolides, triterpenoids, phenanthrenes, sterols, fatty acids and kalanchosine dimalate salt.

The plant *Bryophyllum pinnatum* shows various pharmacological activities. The chemical

constituents present in the various parts of the plant are responsible for these activities shown by the plant (fig 3). The major chemical constituents present in the plant are (fig 4),

- Isocitric acid & citric acid.
- Bufadienolides like bryotoxin A, B, C
- Phenols, Phenylpropanoids and Flavanoids: Syringic acid, caffeic acid, 4-hydroxy-3 methoxy-cinnamic acid, 4-hydroxybenzoic acid, p-hydroxycinnamic acid, paracoumaric acid, ferulic acid, protocatechuic acid, phosphoenolpyruvate, protocatechuic acid.
- Triterpenoids and Steroids: α-amyrin, α-amyrinacetate, β-amyrin, β-amyrinacetate, bryophollenone, bryophollone, taraxerol, pseudo taraxasterol, 1,8-α-oleanane, friedelin, glutinol[17].
- Vitamins including ascorbic acid, riboflavin, thiamine, niacin and minerals such as calcium, zinc and phosphorous are present in the leaves.
- Study on phytochemical constituents present in the ethanol extract of the leaves of *Bryophyllum pinnatum* on GC-MS analysis shows the presence of compounds like, butyrolactone,3,4-Epoxytetrahydrothiophene-,1,1-dioxide,1-Octen-3ol, Benzaldehyde, Oleic acid, Octadecanoic acid, n-Hexadecanoic acid[18].
- Study of *Bryophyllum pinnatum* stem shows the presence of active constituents' alkaloids, flavonoids, saponin, Tannin, phytate, phenol, calcium, magnesium, phosphorous, sodium, and potassium[19].

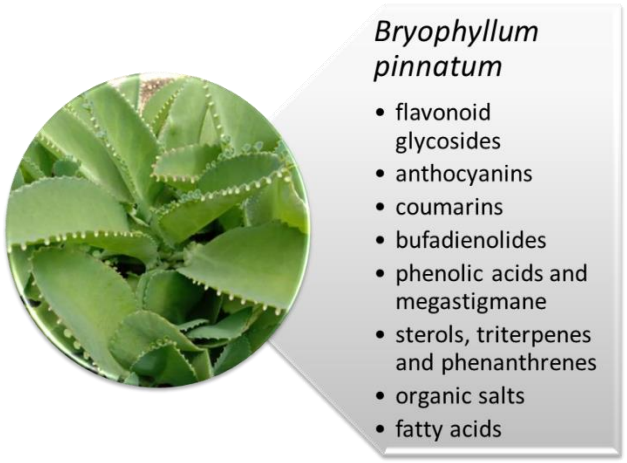
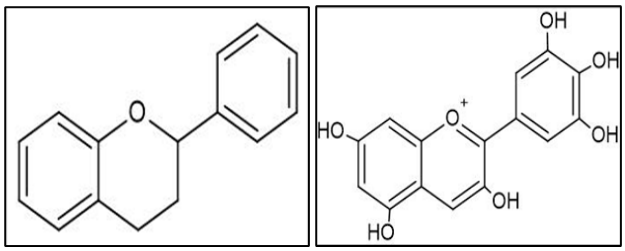


Figure 4: Chemical photoconstitutents

4.1. Flavonoid Glycosides

Flavonoid glycosides isolated from different species of family Crassulaceae are Patuletin-3,7-di-Orhamnoside from *K. spathulata* Leaves & flowers[20], Eupafolin-4'-O-rhamnoside from *K. gracilis* Aerial parts[21], Patuletin-3-O-(4''-O-acetyl- α-L- rhamnopyranosyl)-7-O- (2'''-O-acetyl-α-Lrhamnopyranoside) from *K. brasiliensis* Juice of fresh stems & leaves[22], Quercitrin from *K. pinnata* Fresh leaves[23] and Kaempferitrin from *Bryophyllum pinnatum*[24] *(fig 5a)*.



(a) **(b)**

Figure 5: Chemical structure of (a) flavonoids, (b) anthocyanins

4.2. Anthocyanins

Kalanchoe blossfeldiana varieties with orange, pink, red and magenta flowers contain 3, 5- O-β-D-diglucosides of pelargonidin, cyanidin, peonidin, delphinidin, petunidin and malvidin. Orange varieties contained delphinidin derivatives[25] (fig 5b).

4.3. Coumarins

5-hydroxycoumarin was isolated from the aerial parts of *K. gracilis*[21] (fig 6).

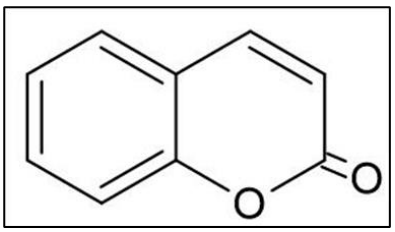
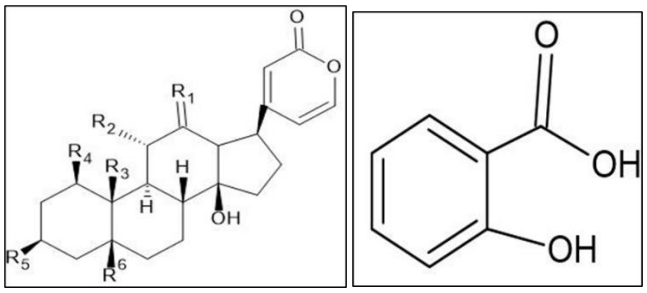


Figure 6: Chemical structure of coumarins

4.4. Bufadienolides

Genus Kalanchoe is reported to contain plant cytotoxic bufadienolides[10,12]. The isolated bufadienolides (fig 7a) from leaves and whole aerial parts from different Kalanchoe species are reported. Hellibrigenin-3- acetate from *K. lanceolata* Leaves[26], Bersaldegenin-1,3,5- orthoacetate from *K. daigremontiana* Leaves[27], Bryophyllin B from *Bryophyllum pinnatum* leaves[28] and Bryophyllin A (Bryotoxic C) from *K. pinnata* Leaves[29].



(a) **(b)**

Figure 7: Chemical structure of (a) bufadienolides, (b) pheolics

4.5. Phenolic Acids and Megastigmane

p-Methoxy benzoic acid, p-hydroxybenzaldehyde, vanillic acid, p-hydroxybenzoic acid, cinnamic acid and nicotinic acid were isolated from the methanol extracts of *K. hybrida*[9]. Protocatechuic-4'-O-β-D-4C1-glucopyranoside was isolated from the ethyl acetate fraction of the leaf aqueous extract of *K. marmorata*[30]. Blumenol A, a megstigmane derivative, was isolated from the methanol extracts of *K. hybrida*[9] (fig 7b).

4.6. Sterols, Triterpenes and Phenanthrenes

Several compounds had been isolated from the fresh leaves of *Bryophyllum pinnatum* , namely bryophyllol, bryophollone and bryophollenone, bryophynol and 18α-oleanane, ψtaraxasterol, along with a mixture of α- and β-amyrins and their acetates[31] and from the whole aerial parts 5α- stigmast- 24-en-3β-ol; 25-methyl- 5α-ergost-24 (27)- en-3β–ol; (24R)- stigmasta- 5, 25- dien- 3β-ol (24-epiclerosterol) and (24R)- 5α- stigmasta- 7, 25-dien-3β-ol were isolated[32]. On the other hand, 3-oxo-olean-12-ene and β-sitosterol has been isolated from the dichloromethane fraction of the leaves of K. thrysiflora[33].

4.7. Organic Salts

Kalanchosine di-malate (KMC) is an anti-inflammatory salt from the fresh juice of the aerial parts of *Kalanchoe brasiliensis*[34].

4.8. Fatty Acids

Palmitic acid (C16), stearic acid (C18) and traces of arachidic (C20) and behenic acids (C22) were identified from the ethanol extract of *Kalanchoe pinnata*[35].

5. PHARMACOLOGICAL PROPERTIES

A review of literature revealed that genus Kalanchoe had several pharmacological activities (fig 8) viz antiviral, sedative, antiulcer, immunomodulatory, antilieshmanial, CNS depressant, antiinflammatory, thyroid peroxidase inhibitor, cytotoxic, hepatoprotective, antioxidant, analgesic, anticonvulsant, antimicrobial, B cell development inhibitor, cardiovascular activity, antihyperglycemic, larvicidal and insecticidal.

5.1. Antiviral Activity

The antiviral properties of the juice of 8 species belonging to the genera Kalanchoe, viz *K. diagremontiona; K. peteri.; K. prolifera; K. marnieriana; K. blossfeldiana; K. beharensis; K. waldheimii* and *K. pinnata* were tested. Only the juice from the 4 latter species had shown high virus neutralizing activity[36].

5.2. Sedative Activity

Both bufadienolides viz daigremontianin and bersaldegenin- 1, 3, 5- orthoacetate that were isolated from K. daigremontiana and K. tubiflora had shown a strong sedative effect in mice at low doses (motility test) and become toxic at higher concentration, inducing paralysis and spasmodic muscle contraction[27].

Figure 8: Pharmacological properties of *Bryophyllum pinnatum*

5.3. Antiulcer Activity

The methanol fraction from the leaf extract of *Bryophyllum pinnatum* possessed significant anti-ulcer activity in nine different experimental animal models. Treating the rats with the methanol extract before the experiment had shown an obvious effect of protection against different ulcerogenic compounds and stress conditions too. Significant protection with extract treatment was observed to occur for aspirin-induced ulcer in pylorus-ligated rats and for histamine-induced duodenal lesions in guinea pigs[37].

5.4. Immunomodulatory Activity

The aqueous extract of *K. pinnata* leaves showed significant inhibition of cell-mediated and humoral immune responses in mice in a model where spleen cells of animals were pretreated with *K. pinnata* leaf extract. A delayed-type hypersensitivity reaction to ovalbumin had been developed by intravenous and topical routes followed by intraperitoneal and oral routes. These indicated that the aqueous extract of *K. pinnata* possesses an immunosuppressive activity[7]. The fractionation of the juice of the fresh stems and leaves of *K. brasiliensis* was monitored by an assay measuring lymphocyte proliferation[22]. Recently, the protective effect of the leaves of K. pinnata in fatal anaphylactic shock, likewise a Th2 type T cell-driven immunopathology was reported. Oral protection in vivo was accompanied by a reduced production of IgE antibodies, reduced eosinophilia and impaired production of the IL-5, IL-10 and TNF-α cytokines. *In-vitro*, *K. pinnata* prevented antigen induced mast cell degranulation and histamine release[13].

5.5. Antileishmanial Activity

The effect of a leaf extract of *K. pinnata* in mice infected with Leishmania amazonensis was investigated. Oral treatment with aqueous leaf extract of *K. pinnata* daily, prevented lesion growth and decreased number of living parasites compared to reference drug, Glucantime. The oral route had showed higher activity compared to other routes[38]. Quercitrin, one of the constituents of the biologically active aqueous extract obtained from *K. pinnata* is demonstrated to be potent antileishmanial compound with a low toxicity profile. This was the first time that antileishmanial activity is demonstrated for a flavonoid glycoside. Also, they identified three flavonoids from the aqueous leaf extract of *K. pinnata* and those were tested separately against Leishmania in comparison with standard flavonoids quercitrin, quercetin and afzelin. Among the important structure activity relationship findings is the role of quercetin aglycone and rhamnosyl unit linked at C-3[23,39]. Lately they indicated that quercetin glycosides are important active components of the aqueous extract and that they possess potent oral efficacy against cutaneous leishmaniasis[40].

5.6. CNS depressant Activity

The methanol fraction of *Bryophyllum pinnatum* leaf extract had produced alteration of behaviour pattern, caused dose-dependent potentiation of pentobarbitone sleeping time and had significant analgesic activity. On the other side reduction of exploratory behaviour and loss of residual curiosity were observed[41].

5.7. Anti-inflammatory Activity

Kalanchoe brasiliensis leaf extracts were obtained before and during the blooming season and then tested for the anti-inflammatory effect on carrageenin-induced rat paw oedema; the leaf extract obtained before blooming showed an inhibitory effect on paw oedema induced by carrageenin while extract obtained during blooming showed no inhibitory effect[9]. Further tests were done to investigate the anti-inflammatory effect of juice obtained from leaves of *K. brasiliensis* on zymosan-induced inflammation. Mice received a subcutaneous injection of zymosan in the footpad. Beginning 2 days after the injection, mice were treated daily for 5 days with different concentrations of lyophilized *K. brasiliensis* juice dissolved in water. Treatment had shown reduced footpad thickness, leukocyte infiltration and blood flow in the footpad area. Popliteal lymph node weight in zymosan-injected mice had also decreased, in comparison with indomethacin[42]. The anti-inflammatory activity of the fresh juice was attributed to the presence of kalanchosine dimalate (KMC), an anti-inflammatory salt[38].

5.8. Thyroid peroxidase inhibitor Activity

The *Kalanchoe brasiliensis* aqueous extract is able to scavenge H_2O_2 in vitro which is an essential thyroid peroxidase (TPO) cofactor. *Kalanchoe brasiliensis* may be responsible for the inhibition of the iodide-oxidation reaction catalyzed by this enzyme by trapping of hydrogen peroxide. Thus, the chronic uptake of the *K. brasiliensis* aqueous extract may lead to the development of goiter and hypothyroidism[43].

5.9. Cytotoxic Activity

The cytotoxic activity of different Kalanchoe species was investigated and tested either for the whole plant extract or the isolated compounds. Bryophyllin B, a potent cytotoxic bufadienolide were isolated from *Bryophyllum pinnatum* and tested against various tumor cells[24]. Five bufadienolides from the leaves of *K. pinnata* and *K. daigremontiana* tubiflora had showed potential cancer chemopreventive activity[44]. The aerial parts of *K. gracilis* had shown cytotoxic activity of against a panel of human tumor cell lines, with potency reaching the nanomolar range. However, few compounds had inhibited HIV replication in H9 lymphocyte cells[45]. The methanol extract of *K. hybrida* towards showed significant cytotoxicity toward MCF-7 (Breast carcinoma cell line) and NCI-H460 (large cell carcinoma of lung cell line) at the tested concentration[9]. The aqueous and the alcoholic extracts of the leaves of *K. thrysiflora* and *K. marmorata* and their fractions (methylene chloride, ethyl acetate and n-butanol) were evaluated for their cytotoxic activity against MCF7 (Breast carcinoma cell line). From the most active cytotoxic fraction, methylene chloride, the cytotoxicity of the isolated compounds was evaluated against normal (HFB4) and cancer (MCF7) cells. 3-oxo-olean-12-ene and β-sitosterol showed similar cytotoxic activity on MCF7 but they were more selective on the cancer cells and not the normal cells HFB4[30].

5.10. Hepatoprotective Activity

The juice of the leaves and the ethanol extract of the marc left after expressing the juice of *K. pinnata* in rats were tested in CCl4-induced hepatotoxicity model. The test material was found effective as hepatoprotective as

evidenced by *in-vitro*, *in-vivo* and histopathological studies. The juice was found more effective than ethanol extract[46].

5.11. Antioxidant Activity

The aqueous extract of *K. pinnata* was evaluated for its protective effects on gentamicin induced nephrotoxicity in rats. *In-vitro* studies revealed that the *K. pinnata* leaf extract possesses significant antioxidant as well as oxidative radical scavenging activities. The aqueous leaf extract of *K. pinnata* may have a nephroprotective effect in case of gentamicin-induced nephrotoxicity[47].

5.12. Analgesic Activity

The analgesic properties of the aqueous and ethanol extracts of the dry leaves of *K. crenata* were evaluated on the pain induced by acetic acid, formalin and by pain induced by pressure on rats' models[48]. While the methylene chloride/methanol (1:1) of *K. crenata* extract and its hexane, methylene chloride, ethyl acetate, n-butanol fractions and aqueous residue were also tested using acetic acid, formalin, and pressure test models. The methylene chloride/methanol (1:1) extract exhibited a significant analgesic activity other than its fractions[49].

5.13. Anticonvulsant Activity

The anticonvulsant effects of methylene chloride / methanol extract of *K. crenata* was evaluated on seizures induced by pentylenetetrazol, strychnine sulphate and thiosemicarbazide. The extract significantly increased the latency period in seizures induced by pentylenetetrazol and significantly reduced the duration of seizures induced by the three convulsant agents. The extract protected 20% of animals against death in seizures induced by strychnine sulphate and thiosemicarbazide[49].

5.14. Antimicrobial Activity

The 60% methanol extract of *Bryophyllum pinnatum* leaf inhibited the growth of Bacillus subtilis, Escherichia coli, Proteus vulgaris, Shigella dysenteriae, Staphylococcus aureus while Klebsiella pneumonia, Pseudomonas aeruginosa and Candida albicans were found to resist the action of the test extract[8]. The activity of the hydroalcohol extracts *K. petitiana*, which was traditionally used in the treatment of various skin disorders, for its antimicrobial activity against different strains of bacteria and fungi was shown to cause different types of skin infections[50]. The antibacterial activity of the methanol extract of *K. farinace* was demonstrated against gram-positive bacteria including multiresistant staphylococcus strains[51]. Different extracts from the leaves of *Bryophyllum pinnatum* and *K. crenata* were screened for their antimicrobial activities. The leaves were extracted by different solvents viz. water, methanol, local solvents such as palm wine, local gin (Seaman's Schnapps 40% alcoholic drink,) and "omi ekan-ogi" (Sour water from 3 days fermented milled maize). Also, one of the methods to prepare an extract was to squeeze raw juice from the leaves. All extracts were lyophilized. Then they were tested against different gram-negative, gram- positive organisms and a fungus using agar well diffusion and broth dilution methods were used to determine the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC); this experiment showed different antimicrobial activities against certain strains[52]. The n-hexane, carbon tetrachloride and chloroform soluble fractions of a crude methanol extract of the whole plant of *Bryophyllum daigremontianum* were subjected to antimicrobial activity and brine shrimp lethality bioassay. The carbon tetrachloride soluble partitionate of the methanol extract exhibited significant antimicrobial activity and the most potent cytotoxic activity[53].

5.15. Inhibition of B cell development Activity

A highly purified compound named kalanchosine dimalate (KMC) was obtained from *K. brasiliensis* inhibited of B cell development in the bone marrow, without affecting the myeloid lineage development. *In-vitro*, KMC inhibited the interleukin-7 dependent proliferation of B cell precursors and do not induce cell death. Thus, results showed that kalanchosine dimalate can selectively affect B cell lymphopoiesis, possibly acting on the IL-7 signaling pathway, opening new perspectives for a potential therapeutic usage of *K. brasiliensis* derived drugs[54].

5.16. Cardiovascular Effects

The effects of the n-butanol extract from the leaves of *K. crenata* were examined on rat blood pressure and guinea pig papillary muscle contraction and action potential. When administered intravenously at different doses, the n-butanol extract of *K. crenata* leaves induced a significant transient fall in blood pressure and reduced cardiac rate for about 10 min. Concomitantly, the extract significantly increased the PR, QRS, and QT intervals of the electrocardiogram (ECG). The n-butanol extract was found to increase the amplitude of electrical contraction of papillary. When tested on the ventricular myocardiac cell action potential, the extract significantly and time dependently delayed the repolarization without affecting the amplitude. The bradycardic effect of the n-butanol extract may result from the increase of the PR, QRS, and QT intervals which are in accord with the delay in action potential repolarization observed in *in-vitro* studies. The data obtained in the *in-vitro* studies suggested that *K. crenata* possess potassium channel blockade properties that may account for its cardiac properties[55].

5.17. Antihyperglycemic Activity

The effect of the water-ethanol extract of *K. crenata* on blood glucose levels was investigated in fasting normal and diet-induced diabetic rats after a short- and medium-term treatment. Diabetes was induced by submitting wistar rats to a hypercaloric sucrose diet over 4 months. The water-ethanol extract of *K. crenata* exhibited significant increase in the insulin sensitivity index compared with the initial time and to the untreated diabetic animals. Animals treated for 4 weeks exhibited a slight resistance in body weight gain and decrease in food and water intake comparable with the glibenclamide effects[56].

5.18. Acetylcholinesterase Inhibition Activity

The extracts of *K. brasiliensis*, K. pinnata and *K. gastonis-bornieri* showed acetylcholinesterase inhibitory effects and a toxic effect on Aedes aegypti larvae[57].

5.19. Insecticidal and Larvicidal Activity

The methanol extract of the leaves of *K. pinnata*[29] and the methanolic extract of the leaves of *K. daigremontiana* and *K. tubiflora* were assessed against the third instar larvae of silkworm (Bombyx mori). The results suggest that the orthoester and α-pyrone moieties of bryophyllin A, bryophyllin B, daigromentianin played an important role in this activity[12]. The extracts of *K. brasiliensis, K. pinnata* and *K. gastonis-bornieri* showed a toxic effect on Aedes aegypti larvae[54].

TOLERABILITY STUDIES:

A retrospective and two randomized prospective clinical studies confirmed good tolerability of *B. pinnatum*. In tocolysis, administration of *B. pinnatum* 5% i.v. and 50% p.o. resulted in less side effects than under treatment with betamimetics. Specifically, the occurrence of palpitations and dyspnea were significantly lower due to a lacking effect on β1-adrenoceptors[58]. In addition, the treatment of 14 pregnant women (Bryophyllum group) with B. pinna tum 50% chewable tablets showed no side effects that were at attributable to the medication[59]. Another study revealed no significant difference in observed side effects. One woman treated with *B. pinnatum* 50% chewable tablets suffered from diarrhoea and dysentery, possibly due to lactose intolerance, and a second woman developed exanthema of the face and upper thorax[60]. In a longitudinal, prospective, randomized, controlled animal study, the effect of the mother tincture (MT), 30% of *B. pinnatum*, in pregnant Wistar rats was investigated. From day 0ofgestation, 60 rats were treated with the *B. pinnatum* MT or pure vehicle. Two control groups, C1 and C2, received an equivalent to the usual daily dose and 25× the maximum daily dose of vehicle, respectively. Groups B1, B2, B3, and B4 received every day 1, 25, 50, and 100× the maximum daily dose of MT, respectively. After 20 days of treatment, weight gain (excluding fetal and placental weight) was higher in group B4 than in groups B1, C2, and B2. However, the perinea in group C1 were heavier than those in group B2. No maternal or fetal deaths, no differences in implantations and resorptions, and no differences in the number and weight of the fetuses and placentas were observed. External fetal abnormalities were not observed in groups B1–B4[61].

6. TOXICITY OF KALANCHOE

The bufadienolides found in Bryophyllum (Kalanchoe) species are toxic to cattle and other farm stocks. Bryophyllum poisoning causes anorexia, depression, ruminal atony, diarrhea, heart rate, rhythm abnormalities, dyspnea and death. Myocardial degeneration and necrosis with hemorrhages of the heart and the alimentary tract have been also observed[62].

B. pinnatum is well tolerated in patients. However, toxicity of Bryophyllum species has been reported to be related to bufadienolides. The cardiotoxic activity of bersaldegenin-1,3,5-orthoacetate (3) was investigated in vitro using isolated rabbit and guinea pig hearts. A strong positive inotropic effect was shown[63,64]. Toxicity to cattle has been documented in earlier studies. A study was conducted including two calves that were treated with the flower heads of *B. pinnatum*. Clinical parameters were examined after administration of 20g/kg b.w. by stomach tube. Five hours after dosing, the animals became depressed and suffered from rumen stasis and anorexia. The first calf died after 9h due to dyspnea and tachycardia. The second calf had diarrhea until it died after 15.5h. This study demonstrated a correlation between bufadienolides and the toxic effect in cattle[65]. An acute toxicity study was performed with a total of 25 rats (or mice, see below), which were given either a *B. pinnatum* methanolic extract or distilled water as a single dose. Mortality was observed after 24h. A dose of 25mg/kg caused neither death nor side effects, but the treatment with 200mg/kg was lethal for 100% of the animals[66]. Unfortunately, information provided in the publication on the route of administration route (oral or intraperitoneal) and the animal species (rats or mice) is contradictory. A similar study was performed including Swiss albino mice. Intraperitoneal administration in mice of aqueous and methanolic extracts showed LD50 values of 957 and 1159mg/kg, respectively. Oral doses up to 3g/kg b.w. in mice and rats led to no signs of toxicity[67]. In mice, an intraperitoneally administered methanolic fraction led to no deaths up to 2500mg/kg b.w. in mice, but their behaviour changed with concentrations >100mg/kg b.w.[68].

Side Effects of *Bryophyllum pinnatum*

Here are some of the potential side effects of *Bryophyllum pinnatum*:

1. **Gastrointestinal distress**: Some people may experience nausea; vomiting, or diarrhea after consuming *Bryophyllum pinnatum*.
2. **Skin irritation**: Applying *Bryophyllum pinnatum* topically can cause skin irritation or allergic reactions in some people.
3. **Uterine contractions**: *Bryophyllum pinnatum* has been traditionally used to induce labour and may cause uterine contractions in pregnant women. Therefore, pregnant women should avoid consuming this plant.
4. **Lowers blood sugar**: *Bryophyllum pinnatum* has been found to lower blood sugar levels, which can be dangerous for people with diabetes who are already taking medication to lower their blood sugar levels.
5. **Interferes with blood clotting**: *Bryophyllum pinnatum* contains compounds that can interfere with blood clotting, which may increase the risk of bleeding in people who are taking blood-thinning medications.

6. **Liver toxicity**: There have been reports of liver toxicity associated with the consumption of *Bryophyllum pinnatum*, especially when taken in large doses.

7. DNA PROFILING

A comparative DNA profiling of samples of fresh leaves of both *K. thyrsiflora* and K. marmorata leaves were established. A 67.66% polymorphism was attained using ten different primers with the most relevant primer used for discrimination being OPB-09 and OPA-11 RAPD primers[29].

8. CONCLUSION

There is an increasing interest worldwide for herbal medicine specially those which had been used in traditional folklore medicine. Lately, deep pharmacological assays had been done to investigate the reason for the biological activities of these plants to correlate their use with their phytoconstituents. This literature survey revealed that genus Kalanchoe had been thoroughly used in traditional medicine in different areas along the world. Also, genus Kalanchoe contains many bioactive constituents as polysaccharides, flavonoids, sterols, organic acids, triterpenoids, phenolic components and bufadenolides. All these phytoconstituents proved to possess different biological activities viz. antimicrobial, analgesic, anti-inflammatory, antiviral, sedative, antiulcer, immunomodulatory, antileishmanial, CNS depressant, thyroid peroxidase inhibitor, cytotoxic activity, hepatoprotective, inhibition of B cell development, cardiovascular effects, antihyperglycemic, acetylcholineesterase inhibitory, and insecticidal. We are confident that further studies may be needed to declare more phytoconstituents and biological activities. Also, clinical trials had not been recorded up till now so we would like to suggest that researchers all over the world may invade this untouchable area of research.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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