Phcog Rev. Vol, 3, Issue 6, 364-374, 2009
Available Online : www.phcogrev.com

PHCOG REV.: Review Article

Bryophyllum pinnatum (Lam.) Kurz.: Phytochemical and Pharmacological Profile : A Review

Anjoo Kamboj[*1], Ajay Kumar Saluja[2]

Guru Gobind Singh College of Pharmacy, Yamuna Nagar-135001 (Haryana), INDIA[1]
A.R. College of Pharmacy, Vallabh Vidhyanagar, 388120 (Gujarat), INDIA[2]
*For Correspondence:shashi_kamboj@sify.com, anjoo73_kamboj@indiatimes.com**

ABSTRACT

Bryophyllum pinnatum (Lam.) Kurz (Crassulaceae) is a perennial herb growing widely and used in folkloric medicine in tropical Africa, tropical America, India, China, and Australia. The divine herb contains a wide range of active compounds, including alkaloids, triterpenes, glycosides, flavonoids, steroids, bufadienolides, lipids and organic acids, have been isolated from this species. The plant is widely used in traditional medicine for the treatment of variety of ailments and well known for its haemostatic and wound healing properties. The pharmacological studies are reviewed and discussed, focussing on that different extracts from this plant have been found to possess pharmacological activities as immunomodulator, CNS depressant, analgesic, antimicrobial, antiinflammatory, antiallergic, antianaphylactic, antileishmanial, antitumorous, antiulcerous, antibacterial, antifungal, antihistamine, antiviral, febrifuge, gastroprotective, immunosuppressive, insecticidal, muscle relaxant, sedative.

However, future efforts should concentrate more on *in vitro* and *in vivo* studies and also on clinical trials in order to confirm traditional wisdom in the light of a rational phytotherapy. The present review is an attempt to highlight the various ethnopharmacological and traditional uses as well as phytochemical and pharmacological aspects of *B. pinnatum* and to discuss them.

KEYWORDS: Alkaloids, *Bryophyllum Pinnatum*, Bufadienolides, Clinical Trials, Flavonoids..

INTRODUCTION

Bryophyllum pinnatum (Lam.) Kurz (Crassulaceae) Synonym: *Kalanchoe pinnata, Pers, Bryophyllum Calycinum Salisb* (1,2); Common names: Zakham-e-hyat, Life plant, air or maternity plant, love plant, Canterbury bells, Cathedral bells, parnabija etc. It is a perennial herb growing widely and used in folkloric medicine in tropical Africa, tropical America, India, China and Australia (3), classified as a weed (4). The plant flourishes throughout the Southern part of Nigeria (5). This is the only *Kalanchoe* species found in South America, however, 200 other species are found in Africa, Madagascar, China and Java. A number of species are cultivated as ornamentals and are popular tropical house plants. In Brazil, the plant goes by the common names of saião or coirama and in Peru it is called hoja del aire (air plant) or *kalanchoe* (6).

The plant grows all over India in hot and moist areas, especially in Bengal. It is a succulent perennial plant that grows 1-1.5 m in height and the stem is hollow four-angled and usually branched. Leaves are opposite, decussate, succulent, 10-20 cm long. The lower leaves are simple, whereas, the upper ones 3-7 foliate and are long-petioled. They are fleshy dark green that are distinctively scalloped and trimmed in red. Leaf blade pinnately compound with 3–5 leaflets, 10–30 cm; petiolules 2–4 cm; leaflet blades oblong to elliptic, 6–8 × 3–5 cm, margin crenate with each notch bearing a dormant bud competent to develop into a healthy plantlet [7], apex obtuse. The leaves are furnished with rooting vegetative buds. Inflorescences terminal paniculate 10–40 cm. Flowers are many bell-like pendulous. Calyx tubular, 2–4 cm; Corolla reddish to purple, 5 cm, base sparsely ciliate; lobes ovate-lanceolate; 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 (6, 8).

It is astringent, sour in taste, sweet in the post digestive effect and has hot potency. It is well known for its haemostatic and wound healing properties. The plant have considerable attention for their medicinal properties and find application in folk medicine, as well as in the contemporary medicine. The present review highlights the various ethnopharmacological uses, phytochemical and pharmacological studies conducted on *B. Pinnatum* and also pinpoints unexplored potential of it (8-10).

ETHNOPHARMACOLOGY

Various species of *B.Pinnatum* are used medicinally in Indo-China and Philippines Islands. It is naturalized throughout the hot and moist parts of India. The leaves and bark are bitter tonic, astringent to the bowels, analgesic, carminative, useful in diarrhoea and vomiting (11). It is applied externally and taken internally for all types of pains and inflammations, various bacterial, viral and fungal infections, leishmaniasis, earaches, upper respiratory infections, stomach ulcers, flu and fever (12).

In traditional medicine, the leaves of this plant have been used for antimicrobial (4,13,14), antifungal (15), antiulcer (16), anti-inflammatory, analgesic (17,18), antihypertensive (19), potent anti-histamine and anti-allergic activity (20). The Creoles use the lightly roasted leaves for cancer, inflammations, and a leaf infusion for fevers. The Palikur mix the leaf juice with

coconut oil or andiroba oil and then rub it on the forehead for migraines and headaches. To the Siona indigenous peoples heat the leaves and apply them topically to boils and skin ulcers. Along the Rio Pastaza in Ecuador, natives use a leaf infusion for broken bones and internal bruises. In Peru, indigenous tribes mix the leaf with aguardiente (sugar cane rum) and apply the mixture to the temples for headaches; they soak the leaves and stems overnight in cold water and then drink it for heartburn, urethritis, fevers and for all sorts of respiratory conditions. The root infusion is also used in epilepsy. Other tribes in the Amazon squeeze the juice from fresh leaves and mix it with mother's milk for earaches.

In Mexico and Nicaragua it is also used to promote menstruation and assist in childbirth. In Nigeria and other West African countries, its fleshy leaves are frequently used as herbal remedy for an array of human disorders, including: hypertension, diabetes mellitus, bruises, wounds, boils, abscesses, insect bites, arthritis, rheumatism, joint pains, headaches and body pains.

The leaves of the plant have great medicinal value and are used both, internally as well externally. The leaves possess various properties like haemostatic, refrigerant, emollient, mucilaginous, vulnerary, depurative, anti-inflammatory, disinfectant and tonic. They are useful in vitiated conditions of vata and pitta, cuts, wounds, hemorrhoids, menorrhagia, discoloration of the skin, boils, sloughing ulcers, ophthalmic, burns, scalds, corn, diarrhea, dysentery (21), headaches (22), vomiting, acute inflammations and bronchitis. It is also employed for kidney stones, gastric ulcers, skin disorders and edema of the legs. Externally, the pulp of the leaves or the juice is applied on traumatic injuries to arrest the bleeding as it contract the minute arterioles and promote the healing of wounds. It is also used for headaches, toothaches, earaches, eye infections, wounds, ulcers, boils, burns and insect bites. On traumatic wounds, the heated leaves are crushed and applied. It reduces the edema and promotes the wound healing without leaving a scar. Internally, the leaves juice and cumin seeds are given along with the double amount of ghee in dysentery. The herb is highly recommended in bleeding disorders, piles and menorrhagia.

The plant are used by the tribals of Kerala for treating cancer symptoms (6, 23). Also plant induce the typical symptoms of cardiac poisoning, but repeated small doses also cause cotyledonosis, an intoxication affecting the nervous and muscular systems of small animals, particularly sheep, in the Karoo area of South Africa (8, 10).

PHYTOCHEMICAL CONSTITUENTS

B.Pinnatum is rich in alkaloids, triterpenes, glycosides, flavonoids, cardienolides, steroids, bufadienolides and lipids (24-27). The leaves contain a group of chemicals called bufadienolides which are very active. 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, antitumorous, cancer preventative and insecticidal actions (10,28-30).

Phenols, Phenylpropanoids and Flavanoids

Syringic acid, caffeic acid **[25]**, 4-hydroxy-3-methoxy-cinnamic acid, 4-hydroxybenzoic acid, p-hydroxycinnamic acid, para-coumaric acid, ferulic acid, protocatechuic acid**,** phosphoenolpyruvate, protocatechuic acid isolated from aerial parts of plants.

Leaves contains astragalin, 3,8-dimethoxy-4,5,7-trihydroxyflavone, friedelin, epigallocatechin-3-o-syringate, luteolin, rutin**[27]**, kaempferol**[23]**, quercetin **[14]**, quercetin-3L-rhamonsido-L-arabino furanoside (29, 39); quercetin-3-O-diarabinoside, kaempferol-3-glucoside (34), kaempferol-3-O-α-L-arabinopyranosyl (1→2)α-L-rhamno pyranoside **[12]**, quercetin-3-O-α-L-arabino pyranosyl(1→2)α-L-rhamno pyranoside **[13]** and 4',5-dihydroxy-3',8-dimethoxy flavone-7-O-β-D-glucopyranoside **[14]**. Because of its restricted occurrence and its abundance in *B. Pinnatum*, flavonoid may be a chemical marker of the plant of high therapeutic potential (40, 41, 53, 54).

Triterpenoids and Steroids

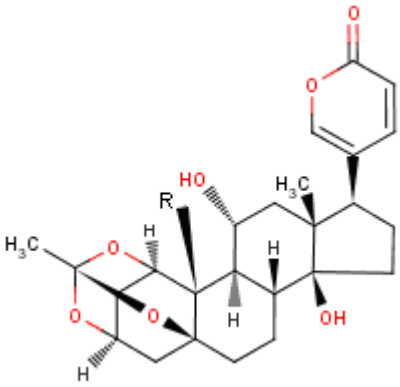
The plant contains α-amyrin, α-amyrinacetate, β-amyrin, β-amyrinacetate, bryophollenone **[8]**, bryophollone **[4]** (29, 38), taraxerol, Ψ-taraxasterol **[24]**, pseudo taraxasterol, 18-α-oleanane, friedelin, glutinol.

The cardienolide and steroidal contents includes β-sitosterol **[17]**, bryophyllol **[5]**, bryophynol **[6]**, bryophyllin B (Antitumor) **[3]** (29-32), bryophyllin A **[1]** (bryotoxin C **[11]**, bufadienolide1,3,5-orthoacetate) with potent cytotoxicity, a insecticidal bufadienolide bryophyllin C **[2]** (34) and bersaldegenin-3-acetate (31-33), bryotoxin A **[9]**, bryotoxin B **[10]**, bersaldegenin-1,3,5-orthoacetate **[7]** (35,36), campesterol **[19]**, 24-ethyl-25-hydroxycholesterol, isofucosterol **[20]**, clionasterol **[29]**, codisterol **[22]**, peposterol, 22-dihydrobrassicasterol **[18]**, clerosterol, 24-epiclerosterol, 24-ethyl- desmosterol **[21]**, 25-methyl-5α-ergost-24(28)-en-3β-ol, ergosta-5-24(28)-dien-3-β-ol, 25-methyl-ergosta-5-24(28)-dien-3-β-ol, 5α-stigmast-24-en-3β-ol , (24s)-stigmast-25-en-3-β-ol, (24r)-5α-stigmasta-7-25-dien-3-β-ol, (24s)-5α-stigmasta-7,25-dien-3-β-ol, 24(R)-stigmasta-5,25-dien-3β-ol, stigmasterol **[16]**, patuletin **[28]**, 3-O-(4-O-acetyl-α-L-rhamnopyranosyl)-7-O-(2-O-acetyl-α-L-rhamno pyranoside) patuletin, 3-O-α-L-rhamno pyranosyl-7-O-(2-O-acetyl-α-L-rhamno pyranoside) patuletin, 3-O-(4-O-acetyl-α-L- rhamno pyranosyl)-7-O-rhamno pyranoside patuletin are isolated from aerial parts (4,30, 37,38).

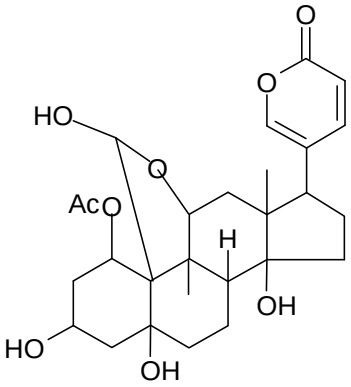
Fatty Acids, Minerals and Others

Fatty acid fraction includes palmitic acid (89.3%), stearic acid (10.7%), traces of arachidic and behenic acid (30,31,42). Plant also contains HCN, oxalic acid (37), citric acid, isocitric acid (45,46), oxaloacetate (42), malic acid (92) and succinic acid. The plant is rich in vitamins and aminoacids; ascorbic acid, riboflavin, thiamine, niacin, pyridoxine, glycine, cysteine, casein hydrolysate, glutamic acid, protein hydrolysate, methionine, tyrosine, phenylalanine (36, 43-45, 50).

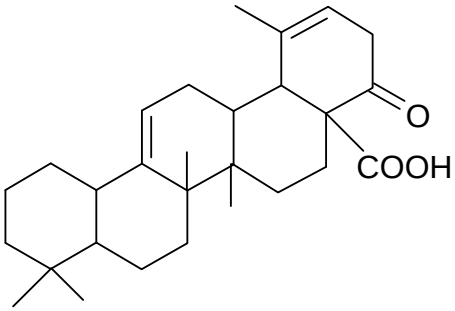
Food contents are carbohydrates, protein, lipids, acids, iodine. The herb is good source of mineral elements such as Na, Ca, K, P, Mg, Mn, Fe, Cu, Zn. Sugar contents includes raffinose, lactose, sucrose, glucose, galactose, fructose**.** Plant also contains alkaloids, tannins, phenanthrene derivatives: 2(9-



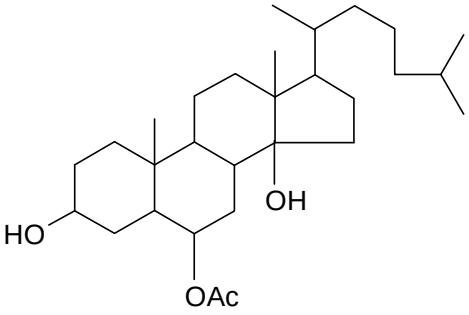
1. Bryophyllin A R=CHO
2. Bryophyllin C R=CH_2OH



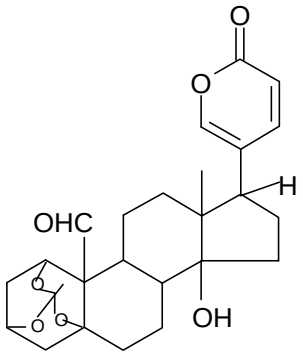
3. Bryophyllin B



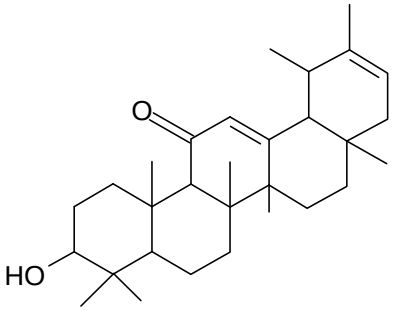
4. Bryophollone



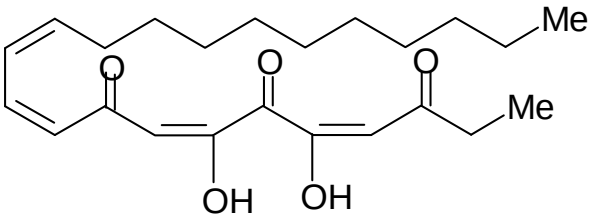
5. Bryophyllol



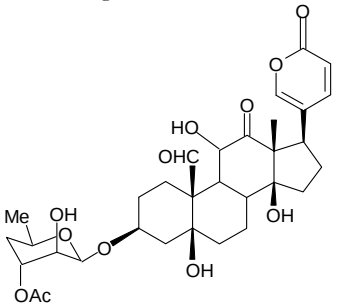
6. Bryphynol



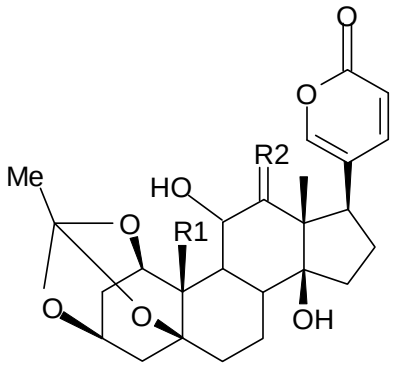
7. Bersaldegenin-1,3,5-orthoacetate



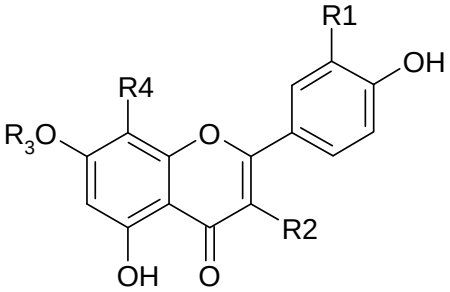
8. Bryphollenone



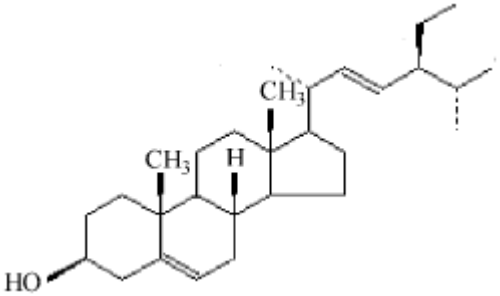
9. Bryotoxin- A



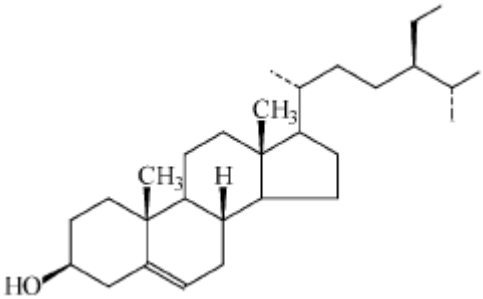
10. Bryotoxin B R1=CH_2OH; R2=O
11. Bryotoxin C R1=CHO; R2= H_2



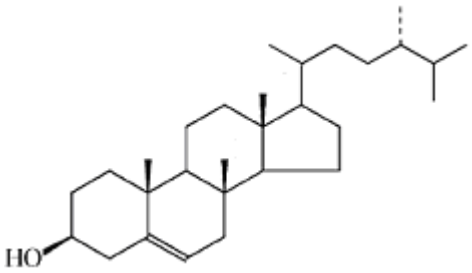
Flavanoids	R_1	R_2	R_3	R_4
12. Kaemferol-3-O--α-L-arabinosyl(1→2) α-L-rhamnopyranoside	H	O-α-L-arabinosyl(1→2) α-L-rhamnopyranose	H	H
13. Quercetin-3-O--α-L-arabinosyl(1→2) α-L-rhamnopyranoside	OH	O-α-L-arabinosyl(1→2) α-L-rhamnopyranose	H	H
14. 4',5-dihydroxy-3',8-dimethoxyflavone-7-O-β-D-glucopyranoside	OMe	H	β-D-glucospyranose	OMe
15. Quercitrin	OH	α-L-rhamnopyranose	H	H



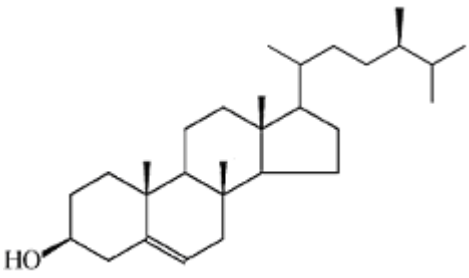
16. Stigmasterol



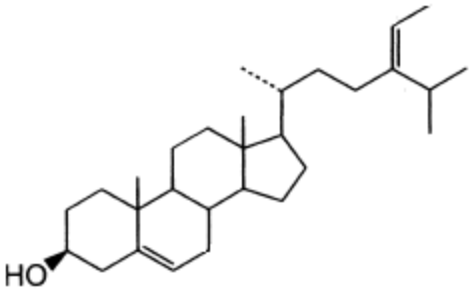
17. β – Sitosterol



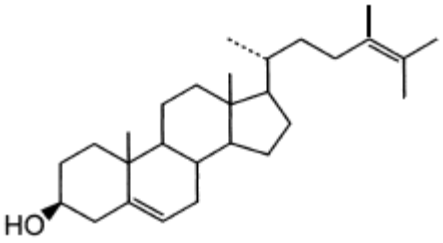
18. Dihydrobrassicasterol



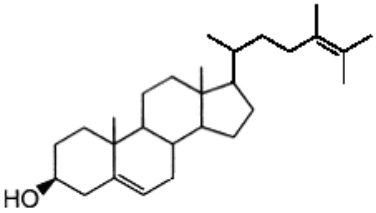
19. Campesterol



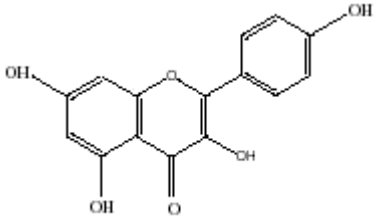
20. Isofucosterol



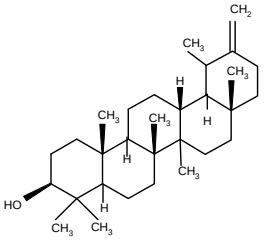
21. 24-methyl-desmosterol



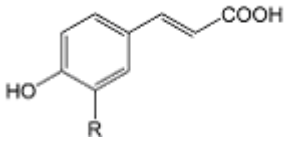
22. Codisterol



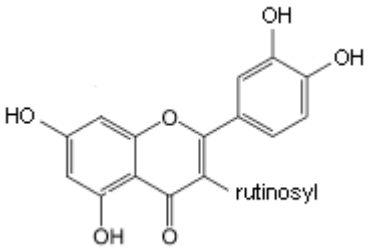
23.Kaempferol



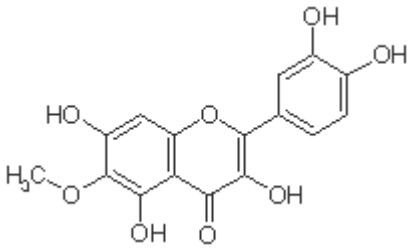
24. Taraxasterol



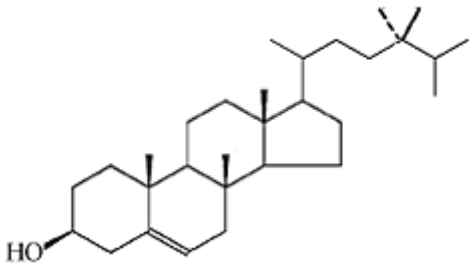
25. Caffeic acid R=OH
26. Ferulic acid R= OCH_3



27. Rutin



28. Patuletin



29. Clionosterol

decenyl)-phenanthrene, 2(9-undecenyl)-phenanthrene, alkanes (C_{25-35}), alkanols (C_{26-34}), n-triacontane, hentriacontane (37, 38, 43, 50).

PHARMACOLOGICAL ACTIVITIES

Herbal Tonic

The plant is good sources of ascorbic acids, riboflavin, thiamine and niacin. Natural ascorbic acid is vital for the body performance i.e. normal formation of intercellular substances throughout the body, including collagen, bone matrix and tooth dentine (47, 48). Therefore, the clinical manifestations of scurvy that is hemorrhage from mucous membrane of the mouth, gastrointestinal tract, anemia, pains in the joints can be related to the association of ascorbic acid and normal connective tissue metabolism (48). This function of ascorbic acid accounts for its normal wound healing property. As a result the plant is used in herbal medicine for the treatment of common cold and other diseases like prostrate cancer (47, 49, 50). In a study an herbal composition comprised of extracts of number of herbs including *B.Pinnatum* acts as a tonic to improve respiration, aid in the elimination of toxins and improves overall vitality (51).

Antileishmanial activity

Infections caused by protozoa of the genus *Leishmania* are a major worldwide health problem, with high endemicity in developing countries. The incidence of the disease has increased since the emergence of AIDS. In the absence of a vaccine, there is an urgent need for effective drugs to replace/supplement those in current use. L.G. Rocha et al refered in a review on a plant extracts that a chemically defined molecules (coumarin, quercetin) of natural origin showing antileishmanial activity (52).

Quercitrin, a flavonoid is responsible for the antileishmanial activity of *B.Pinnatum*. The quercetin aglycone-type structure, as well as a rhamnosyl unit linked at C-3, seem to be important for antileishmanial activity (54). Da Silva et al investigated the antileishmanial properties of three flavanoids (quercitrin, quercetin and afzelin) of leaf extract in mice against *L. amazonenis* amastigotes and found oral route was more effective than other (i.v. or tropical) routes. The protective effect of plant in leishmaniasis may not be due to a direct effect on the parasite itself but rather activation of the reactive nitrogen intermediates pathway of macrophages (12, 53).

Hepatoprotective and Nephroprotective

Juice of the fresh leaves is used very effectively for the treatment of jaundice in Bundelkhand region of India. Yadav et al studied that the juice of leaves was found more effective than ethanolic extract as evidenced by invivo and invitro histopathological studies for hepatoprotective activity of plant and justifies the use of juice of plant leaves in folk medicine for jaundice (56). The protective effect on gentamicin-induced nephrotoxicity in rats which may involve its antioxidant and oxidative radical scavenging activities (57).

Neuropharmacological activities

B.Pinnatum has been used since 1921 in traditional medicine as an antipsychotic agent (20, 54, 55). Salahdeen et al showed that the aqueous leaf extract possesses depressant action on CNS. The animals treated with 50 -200mg/kg was found to produce quite significant decrease in locomotor's activity in dose dependent manner, with no ptosis at these doses. Similarly in chimney, climbing and inclined screen tests, there was a significant loss of coordination and decrease muscle tone in animals treated intraperitoneally with aqueous extract in a dose dependent fashion. The result indicates significant alterations in general behaviour pattern, reduction in spontaneous mortality, potentiation of pentobarbitone-induced sleeping time in a dose dependent fashion (55-59,65). Pal et al in his study found that the anticonvulsant effect of the aqueous leaf extract observed decrease or no effect compare to methanolic extract. The methanolic fraction possesses a potent CNS depressant action. As alcohol is known to have depressant effect on respiration related hypoglossal nerve output in humans and other mammals. It is possible therefore that the inhibitory effect of methanolic extract on CNS activities may be due to effect of methanol and partly to the constituent of *B.Pinnatum* with its attendant higher dose (59-63).

Bufadienolide has been reported to be poisonous, and it is similar to cardiac glycoside poisoning. Several studies shows that bufadienolide toxin is manifested primarily by digitalis toxicity-like cardiac effects, including bradycardia, A-V conduction block, ventricular tachycardia, ventricular fibrillation and sudden death. Radford et al investigated that the CNS depressant activity of aqueous leaf extract could be due to the presence of bufadienolide and other water soluble constituents in the extract (64).

Yemitan et al investigated with saline leaf extract and found dose dependent CNS depressant effects (pentobarbitone-induced sleep), exploratory activity (Hole-board method, Evasion), muscle relaxant test (Chimney, Traction, Climbing, Inclined Screen tests), anticonvulsant tests (strychinine-induced convulsion, picrotoxin-induced convulsion) (66). Thus the herb possesses remarkable central depressant, skeletal muscle and minor anticonvulsant actions with an acute toxicity higher than 500mg/Kg and 2000mg/Kg when given intraperitoneally and orally (64,65).

Antimutagenic activity

Plant has potent antihistamine and antiallergic activity. The methanol extract of the leaves has also been reported to have histamine receptor (H1) antagonism in the ileum, peripheral vasculature and bronchial muscle (20) and protect against chemically induced anaphylactic reactions and death by selectively blocking histamine receptors in the lungs (68,69). Quercetin-3-o-α-L-arabinopyranosyl(1→2)-α-L-rhamnopyrano -side showed anti allergic activity in rats (70). Obaseiki-Ebor et al investigated that organic solvent extracts of leaves had inhibitory activity for His^- to His^+ reverse-mutations induced by ethyl methanesulfonate acting on S. typhimurium TA100 or TA1002 and were also active against reversions induced by 4-nitro-o-phenylenediamine and 2-aminofluorene in TA98. The alkaloidal/ water soluble and acid fraction had no appreciable antimutagenic activity (67).

Anti-ulcer activity

Flavonoids, the potent water-soluble antioxidants and free radical scavengers, which prevent oxidative cell damage, have

strong anticancer activity (16,47,71,72). Supratman et al investigated on antitumor promoting activity of bufadienolides separated from *B. pinnatum* and found bryophyllin A has most marked inhibition and bersaldegenin-3-acetate is less active (93). Bersaldegenin-1,3,5-orthoacetate inhibited growth of several cancer cell lines (32,33). As antioxidants, flavonoids from these plants provide anti-inflammatory activity (47) and are used for the treatment of wounds, burns and ulcers in herbal medicine. Pal et al revealed that a methanolic fraction of leaves was found to possess significant antiulcer activity. Premedication tests in rats revealed that the extract possessed significant protective action against the gastric lesions induced by aspirin, indomethacin, serotonin, reserpine, stress and ethanol; also significant protection for aspirin-induced ulcer in pylorus-ligated rats and for histamine-induced duodenal lesions in guinea pigs; and also significant enhancement of the healing process was also found to occur in acetic acid-induced chronic gastric lesions in rats (16). Adesanwo et al in his study showed a significant reduction in incidence of ulceration and mean basal and histamine stimulated gastric acid secretion in a dose dependent manner thus justifying its use as an anti-ulcer agent in folklore medicine (73).

Antibacterial activity

The presence of phenolic compounds indicate that the plant possess anti-microbial activity. Ofokansi et al. (2005) reported that plant is effective in the treatment of typhoid fever and other bacterial infections, particularly those caused by *S. aureus, E. coli, B. subtilis, P. aeruginosa, K. aerogenes, K. pneumoniae and S. typhi*. In his study antibacterial activities of the infusion and methanolic extracts against *S. aureusi ATCC 13709, E.coli ATCC 9637, Bacillus, P. aeroginosa, K. pneumonia* and *S. typhi* using the agar diffusion method; also against *S. aureus, E. coli, S.typhi,, Klebsiella spp* and *P.aeruginosa* using a modification of checkerboard method. These findings supported its use in treating the placenta and navel of newborn baby, which not only heals fast but also prevent the formation of infections (49, 74,75). Pure isolated alkaloids and their synthetic derivatives are used as basic medicinal agents for their analgesic, antispasmodic and bactericidal effects (47).

Obaseiki-Ebor et al investigated the invitro antibacterial activity of leaf juice. The extract at 5% v/v was found to bactericidal to a wide spectrum of gram-positive and gram-negative bacteria such as *B. subtilis, S.aureus, S. pyogenes, S.faecalis, E.coli; Proteus spp; Klebsiella spp; Shigella spp; Salmonella spp; S. marcescens;* and *P. aeruginosa* including the clinical isolates of these organisms possessing multiple antibiotic resistance [76]. Schmitt et al showed the antimicrobial activity of decoct of leaves against gram-positive bacteria by dilution tube method (74). Akinpelu in a study found that 60% methanolic leaf extract inhibits the growth of five out of eight bacteria used, at a concentration of 25mg/ml. *B. subtilis, E. coli, P. vulgaris, S. dysentriae, S. aureus* were found to inhibited, while *K. pneumoniae, P.aeruginosa* and *C. albicans* were found to resist the action of the extract (14).

Antidiabetic Activity

The presence of zinc in the plants could mean that the plants can play valuable roles in the management of diabetes, which result from insulin malfunction (50, 74). Ojewole evaluated the antinociceptive effect of the herb's aqueous leaf extract by the 'hot-plate' and 'acetic acid' test models of pain in mice. The anti-inflammatory and antidiabetic effects of the plant extract were investigated in rats, using fresh egg albumin-induced pedal oedema, and streptozotocin -induced diabetes mellitus. The aqueous leaf extract produced significant ($P<0.05$-0.001) antinociceptive effects against thermally and chemically-induced nociceptive pain stimuli in mice. The plant extract also significantly ($P<0.05$-0.001) inhibited fresh egg albumin-induced acute inflammation and cause significant hypoglycaemia in rats. The different flavonoids, polyphenols, triterpenoids and phytosterols of the herb are speculated to account for the observed antinociceptive, anti-inflammatory and antidiabetic properties of the plant. It exert antinociceptive and anti-inflammatory effects probably by inhibiting the release, synthesis and /or production of inflammatory cytokines and mediators, including: prostaglandins, histamine, polypeptide kinins and so on (79).

Immunosuppressive effect

The fattyacids present in *B.Pinnatum* may be responsible atleast inpart, for its immunosuppressive effect invivo (42). Rossi-Bergmann et al showed the aqueous extract of leaves cause significant inhibition of cell-mediated and humoral immune responses in mice. The spleen cells of animals pre-treated with plant extract showed a decreased ability to proliferate in response to both mitogen and antigen in vitro. Treatment with extract also impaired the ability of mice to mount a delayed-type hypersensitivity reaction (DTH) to ovalbumin. The invitro and topical routes of administration were the most effective by almost completely abolishing the DTH reaction. The intraperitoneal and oral routes reduced the reaction by 73% and 47% of controls, respectively. The specific antibody responses to ovalbumin were also significantly reduced by treatment. Thus the aqueous extract of leaves possesses immunosuppressive activities (80). Almeida et al in an investigation also found that leaf extracts inhibited invitro lymphocyte proliferation and showed invivo immunosuppressive activity (42, 81). An attempt to identify the immunosuppressive substances present in *B.Pinnatum* guided by the lymphoproliferative assays. From the ethanolic extract a purified fraction (KP12SA) found twenty-fold more potent to block murine lymphocyte proliferation than the crude extract. Thus provides evidence that saturated fatty acids present in herb plays an important role on lymphocyte proliferation, which explain its immunosuppressive effect in vivo (80).

Antihypertensive activity

Herb possesses hypotensive activity and lend credence to the folkloric use of the herb in the management of hypertension. The plant commonly used in the management of all the types and grades of hypertension by some Yorubas of Western Nigeria. Calcium was the most abundant macro element present in the plant. Normal extracellular calcium concentrations are necessary for blood coagulation and for the integrity, intracellular cement substances (78). The lower sodium content of *B.Pinnatum* might be an added advantage

due to the direct relationship of sodium intake with hypertension on human (83).

Ojewole evaluated the antihypertensive efficacy of leaf extracts. The effects of aqueous and methanolic leaves extracts were examined on arterial blood pressures and heart rates of normal and spontaneously hypertensive rats, using invasive and non-invasive techniques. Both the extracts produced doserelated, significant decreases in arterial blood pressures and heart rates of anaesthetized normotensive and hypertensive rats. The hypotensive effects of the leaves extracts were more pronounced in the hypertensive than in normotensive rats. The leaves extracts also produced dose dependent, significant decreases in the rate and force of contractions of guinea-pig isolated atria, and inhibited electrical field stimulation (ES)-provoked, as well as potassium and receptor-mediated agonist drugs-induced contractions of the rat isolated thoraxic aortic strips in a non-specific manner. cardiodepression and vasodilation would appear to contribute significantly to the antihypertensive effect of the herb (19, 79).

Analgesic, Anti-inflammatory and Wound Healing activity

The high saponin content justifies the use of the extracts to stop bleeding and in treating wounds. Saponin has the property of precipitating and coagulating red blood cells. Some of the characteristics of saponins include formation of foams in aqueous solutions, hemolytic activity, cholesterol binding properties and bitterness (47, 84).These properties bestow high medicinal activities on the extracts from *B.Pinnatum*. Tannins have astringent properties, hasten the healing of wounds and inflamed mucous membranes. These perhaps, explain why traditional medicine healers in Southeastern Nigeria often use herb in treating wounds and burns (85). Dra Amalia et al investigated the anti-inflammatory activity of the fluid extract of the leaves against the edema caused by carrageen in rats. It was confirmed that the fluid extract with 4.5 % of total solids at doses of 100 mg/kg of weight has an anti-inflammatory effect (50, 71, 86, 87).

Aqueous extract of *B.Pinnatum* can demonstrate strong analgesic potency comparable in a time and dose-dependent manner to a non steroidal anti-inflammatory drug. Igwe et al investigated that the aqueous extract was devoid of severe toxic effects, increased the pain threshold in rats using the hot plate or thermal methods, inhibited or reduced phenylbenzoquinone-induced writhing or abdominal stretches in mice in a dose-dependent manner, and produced a weak or an inferior anti-inflammatory activity than aspirin (82).

Uterine Contractility

B. Gwehenberger et al characterise the phytotherapeutic tocolytic effect of *B.Pinnatum* in vitro versus the conventional betamimetic, fenoterol, in human myometrium. Contractility was measured in strips of term myometrium biopsied at caesarean section in 14 women and exposed to increasing concentrations of *B.Pinnatum* versus +/- oxytocin 1 U/l. Result state inhibition of spontaneous contraction was concentration dependent. *B.Pinnatum* increased contraction frequency by 91% at constant amplitude and inhibited oxytocin stimulated contractions by 20% at constant amplitude with slightly decreased frequency. Fenoterol decreased contraction by 50% with a significant decrease in frequency (88).

B.Pinnatum is more effective and has less side effects than traditional labor inhibitors in preventing preterm delivery. In a study Plangger et al compare the tolerability and tocolytic effects between i.v. infused plant extract and beta-agonists. In a retrospective study, 67 pairs of pregnant women in preterm labor treated with i.v. *B.Pinnatum* or beta-agonists were closely matched for maternal age, gestational age at tocolysis, CTG recorded contractions, cervical effacement, preterm premature rupture of the membranes, and history of preterm labor. Results shows that pregnant women with extract and betaagonists were equal in the prolongation of pregnancy (6.2 versus 5.4 days, NS), the gestational age at delivery (38.0 versus 37.1 weeks, NS) and the duration of hospitalisations, but had less adverse effects (34.3 versus 55.2% with palpitation or dyspnea). The neonatal outcome and morbidity in the *B.Pinnatum* group were equal or better. Therefore concluded in the management of preterm labor herb is no less effective than beta-agonists, but is significantly better tolerated (89).

The plant should not be used in pregnancy. Though not supported by clinical research, it has traditionally been used during childbirth and may stimulate the uterus. Also because of immune modulating actions, should not be used chronically for long periods of time, or by those with a lowered immune system.

Toxic to cattle

Mckenzie et al investigated that cardiac glycoside poisoning was produced in calves given flower heads of the hybrid *Bryophyllum Species* and found that for each plant (except *B. tubiflorum*), 2 calves were each given a single dose of 20 g wet weight per kg bodyweight. The results of the calf toxicity experiment with the amounts of bufadienolide measured in the plants suggests that bryotoxins A, B and C probably account for the observed disease (28,90).

Insecticidal, Fungitoxic and Phytotoxic activity

Supratman et al isolated bufadienolides: bryophyllin A and bryophyllin C from *B. Pinnatum* and showed strong insecticidal activity against third instar larvae of the silkworm (93).

Alabi et al studied to evaluate the fungitoxic and phytotoxic effects of extracts on the fungal pathogens inducing wilting on cowpea grown in Ago-Iwoye, South Western Nigeria. The extract reduces the Disease Infection Rate (DIR) in treated plants. *Sclerotium rolfsii sacc* induced wilting of between 4 and 12% on cowpea seedlings treated with plant extract under field conditions while about 39.6% incidence of cowpea seedlings wilting was observed under control experiment on the same experimental plot. The extracts increased significantly the plant height, shelf life, relative water content and chlorophyll contents of the cowpea seedlings during both the wet and dry season. On the other hand, the extracts significantly reduced transpiration rate and stomata aperture of treated plant in both seasons. Furthermore, application of these extracts on the cowpea plants significantly enhanced the Leaf Area Index (LAI), number of branches and pods per plant, total dry matter per plant, weight per pod, 100 grains weight and grain

yield in both season. The extracts also inhibited the release of current photosynthethates from treated plants thus maintaining the water status of plant and also making photosynthethates which can be oxidized to release energy needed for growth available to treated plants (91).

CONCLUSION

The *B. Pinnatum* is widely used divine herb. Modern pharmacological studies have generally confirmed the traditional use of *B. Pinnatum* and their extracts in ailments: inflammations, ulcers, fungal, viral and microbial infections, an impaired immune system, diabetes mellitus, spasms and insecticidal properties. It is believed that detailed information as presented in this review on its phytochemical constituents and various biological properties of extracts and the constituents might provide incentive for evaluation of the use of the plant in medicine and in agriculture. Extracts and fractions tested on mice and rats showed significant analgesic, anti-allergic, anti-anaphylactic, anti-inflammatory, anti-leishmanial, anti-tumorous, anti-ulcerous, antibacterial, antifungal, antihistamine, antiviral, CNS depressant, febrifuge, gastro protective, immunosuppressive, immunomodulator, insecticidal, muscle relaxant, sedative results without adverse side effects. Some small companies in India and Amazon are using *B. Pinnatum* as raw materials for phytochemicals.

The pharmacological studies so far have mostly been performed *in vitro* and *in vivo* with animals. In future study, the isolated principles and *B.Pinnatum* needs to be evaluated in scientific manner using specific animal models and clinical studies are urgently needed in order to confirm traditional wisdom in the light of a rational phytotherapy on the toxicity of plant and especially on bufadienolides and its use during pregnancy and also to understand the molecular mechanism of action, in search of lead molecule from natural resources. It could be concluded that *B. Pinnatum* is a rich source of compounds, interesting chemical structures and various biological active products.

REFERENCES

1. R.N. Chopra, S.L. Nayar, and I.L. Chopra. Glossary of Indian Medicinal Plants. NISCIR (CSIR). New Dehli. **42**: (2002).
2. R.P. Rastogi, and B.N. Mehrotra. Compend. Indian Med. Plants. PID. New Dehli. **2**: 112 (1991).
3. A. Engler. Die naturrlichen Pflanzenfamilien nebst ihren Gattugen and wichtigen Arten insbesondre der Nutpflanzen. Leipzig: W. Engelmann. 402-412 (1926).
4. B. Oliver-Bever. Medicinal plants in tropical west Africa III Antinfection therapy with higher plants. *J. Ethnopharmacology*. **9**: 1-83 (1983).
5. L.S.Gill. Ethno-medical uses of plant in Nigeria: UNIBEN Press. 46: (1992).
6. P. Paranjpe. Indian Medicinal Plants forgotten Healers. Chaukhamba Sanskrit Pratisthan, Delhi. 194-195(2005).
7. S. Jaiswal, and S. Sawhney. Correlation of epiphyllous bud differentiation with foliar senescence in crassulacean succulent *Kalanchoe pinnata* as revealed by thidiazuron and ethrel application. *J. of Plant Physiology*. **163**: 717-722(2006).
8. V.P.S. Varier's. Indian Medicinal Plants a compendium of 500 species. Orient Longman. **3**: 282-284(2002).
9. T.W. Naude. The occurrence and significance of South African cardiac glycosides. *J. S. Afr. Biol. Soc*. **18:** 7(1977).
10. P.S. Steyn, and F. R. Van Heerden. Bufadienolides of plant and animal origin. *Natural Product Reports*. 397-413(1998).
11. K.R. Kirtikar, and B.D. Basu. *Indian Medicinal Plants, periodical experts*. Delhi. **2**: 2nd ed: 999 (1975).
12. S.A. Da Silva, S.S. Costa, S.C. Mendonca, E.M. Silva, V.L. Moraes, and B. Rossi Bergmann. Therapeutic effect of oral *Kalanchoe Pinnata* leaf extract in murine leishmaniasis. *Acta Tropica*. **60** (3): 201-210(1995).
13. Mehta and J.U. Bhat. Studies on Indian Medicinal plant II, bryophyllin, a new antibacterial substance from leaves of *Bryophyllum, Calycinum Salsib. J university Bombay*. **21**: 21-25(1952).
14. D.A. Akinpelu. Antimicrobial activity of Bryophyllum Pinnatum leaves *Fitoterapia*. **71(**2): 193-194 (2000).
15. S. Misra, and S.N. Dixit. Antifungal activity of leaf extract of some higher plants. *Acta Botanica Indica*. **7**: 147-150 (1979).
16. S. Pal, and A.K. Nag Chaudhari. Studies on the Anti-Ulcer activity of a Bryophyllum Pinnatum leaf extract in experimental animals. *J. Ethnopharmacol*. **33**: 97-102(1991).
17. S. Pal, and A.K. Nag Chaudhari. Preliminary studies on the anti-inflammatory and analgesic activities of Bryophyllum pinnatum. *Med Sci Res*. **17**: 561-562(1989).
18. S. Pal, and A.K. Nag Chaudhari. Further studies on anti-inflammatory profile of the methanolic fraction of the fresh leaf extract of *Bryophyllum pinnatum*. *Fitoterapia*. **63**: 451-459(1992).
19. J.A.O. Ojewole. Antihypertension properties of *Bryophyllum pinnatum (Lam)* (oken) leaf extracts. *Am J. Hypert*. **15(4):** A34-A39 (2002).
20. S. Pal, T. Sen, and A.K. Nag Chaudhari. Neuropsychopharmacological profile of the methanolic fraction of *Bryophyllum Pinnatum* leaf extract. *J. Pharm. Pharmacol*. **51**: 313-318(1999).
21. J.M. Dalzeil. The useful plants of west tropical Africa.London: Crown Agents for the colonies. 28-29(1937).
22. A. Sofowora. Medicinal plants and traditional medicine in Africa. New York: John Wiley and Sons. 119 (1993).
23. P.J. Mathew, and M.C. Unithan. Search for plants having anticancer properties used by the tribals of Wyandu, Malappuram and Palghat districts of Kerala. *Indian Aryavaidan*. **6:** 54-60(1992).
24. P.B. Marriage, and D.G. Wilson. Analysis of Organic acids of Bryophyllum pinnatum. *Can. J. Biochem*. **49**: 282-295(1971).
25. K. Gaind, and R. Gupta. Alkanes ,Alkanols, Triterpenes, and Sterols of Kalanchoe Pinnata. *Phytochemistry*. **11:** 1500-1502 (1972).
26. K. Gaind, and R. Gupta. Identification of waxes from leaves of *Kalachoe pinnata. Planta Medica*. **23:** 193-197(1974).
27. S. Costa, A. Jossang, and B. Bodo. Propietes biologiques et phytochiie des *Kalanchoe pinnata*, Systematique ecophysiologie et phytochimie Paris: Karthala. 219-235 (1995).
28. R.A. McKenzie, F.P. Franke, and P.J. Dunster. The toxicity to Cattle and Bufadienolide content of six Bryophyllum species. *Aust Vet J*. **64** (10): 298-301(1987).
29. T. Yamagishi, M. Haruna, X.Z. Yan, J.J. Chang, and K.H. Lee. Antitumor agents, 110, Bryophyllin B, A Novel Potent cytotoxic Bufadienolide from *Bryophyllum Pinnatu.m J. Nat. Prod*. **52(5):** 1071-1079(1989).
30. R.P. Rastogi, and B.N. Mehrotra. Compendium of Indian Medicinal Plants. 5: 141-143 (1990-1994).
31. Y. Takashi, Y. Xiu-Zhen, Rong-Yang, M.R. Donald, and M.L. Kuo-Hsiung. Chem Structure and stereochemistry of Bryophyllin A, A novel potent cytotoxic Bufadienolide orthoacetate from *Bryophyllum pinnatum*. *Pharm Bull*. **36** (4): 1615-1617 (1988).
32. X. Yan, K. Lee, and T. Yamagishi. Isolation and identification of cytotoxic components from *Bryophyllum Pinnatum*. *Shanghai Yike Daxue Xuebao*. **19(3)**: 206-208 (1992).
33. Chem.abst. 117: 188260w (1992).
34. U. Supratman, T. Fujita, K. Akiyama, and H. Hayashi. New insecticidal bufadienolide, Bryophyllin C from *Kalanchoe pinnata. Biosci Biotechnol Biochem*. **64**(6): 1310-1312(2000).
35. Chem Abst. 113:118355(1990).
36. D.A. Alabi, M.Z. Onibudol, and N.A. Amusa. Chemicals and Nutritional Composition of Four Botanicals with Fungitoxic Properties. *World J of Agri Sci*. **1**: 84-85 (2005).
37. S. Siddiqui, S. Faizi, B.S. Siddiqui, and N. Sultana. Triterpenoids and Phenanthrenes from leaves of *Bryophyllum Pinnatum. Phytochemistry*. **28(9)**: 2433-2438 (1989).
38. A. Toshihiro, K. WCMC, T. Toshitake, and M. Taro. Sterols of Kalanchoe pinnata. First report of the isolation of both C-24 epimers of 24-Alkyl-Δ25-sterol from higher plants. *Lipids*. **26:** 660 (1991).

39. Chem. Abstr. 73: 84621w (1970).
40. Chem..Abstr. 105: 178423q (1986).
41. F. Michelle, A. Muzitano, W. Luzineide, A. Tinoco, B. Catherine Guette, R. Carlos, C. Kaiser, D. Bartira Rossi-Bergmann, S. Soˆnia, and A. Costa. *Phytochemistry*. **67:** 2071–2077(2006).
42. A.P. Almeida, S.A.G. Da Silva, M.L.M. Souza, L.M.T.R. Lima, B. Rossi-Bergmann, V.L. Gonçalves de Moraes, and S.S. Costa. Isolation and Chemicals análisis of a fatty acid fraction of *Kalanchoe Pinnata* with a potent lymphocyte suppressive activity. *Planta Medica*. **66**: 134-137 (2000).
43. D.E. Okwu, and C. Josiah. Evaluation of the chemical composition of two Nigerian medicinal plants. *African Journal of Biotechnology*. **5(4):** 357-361(2006).
44. R.P. Rastogi, and B.N. Mehrotra. Compend. of Indian Med Plants. CDRI Lucknow and PID New Delhi. **1**: 63-64 (1960-1969).
45. Chem abstr. 120:4592P (1994).
46. G.W. Pucher, M.D. Abrahams, and H.B. Vickery. The preparation of optically active Isocitric acid from Bryophyllum leaf tissue. *J. of Biological Chemistry*. 579-588.
47. D.E. Okwu, and M.E. Okwu. J. *Sustain Agric. Environ*. **6(2):** 140-147 (2004).
48. S. Hunt, I.L. Groff, and J. Holbrook. Principles and Chemical Practice. John Wiley and sons New York. 459-462 (1980).
49. D.E. Okwu. *Nig. Agric.J*. **34**: 143-148 (2003).
50. S. Pal, A.K. Nag, and N. Chaudhari, Anti-inflammatory action of *Bryophyllum pinnatum* leaf extract. *Fitoterapia*. **61**: 527-533 (1990).
51. K.C. Ofokansi, C.O. Esimone, and C.R. Anele. *Plant Products Research Journal*. **9**: 23-27 (2005).
52. L.G. Rocha, J.R.G.S. Almeida, R.O. Macedo, and J.M. Barbosa-Filho. A review of natural products with antileishmanial activity. *Phytomedicine*. **12**: 514–535 (2005).
53. S.A.G. Da-Silva, S.S. Costa, and B. Rossi-Bergmann. The anti-leishmanial effect of Kalanchoe is mediated by Nitric Oxide intermediates. *Parasitology*. **118 (6)**: 575-582 (1999).
54. M.F. Muzitano, W.T. Luzineide, G. Catherine, C.R. Kaiser, B. Ross-Bergmann, and S.S. Costa. The antileishmanial activity assessment of unusual flavonoids from *Kalanchoe pinnata*. *Phytochemistry*. **67:** 2071–2077 (2006).
55. B.R. Rossi, E.C. Torres-Santos, A.P.P.T. Santos, A.P. Almeida, S.S. Costa, and S.A.G. Da-Silva. Treatment of cutaneous leishmaniasis with *Kalachoe pinnata*: Experimental and clinical data. *Phytomedicine*. **7**: 115 (2000).
56. N.P. Yadav, and V. K. Dixit. Hepatoprotective activity of leaves of *Kalanchoe Pinnata Pers.*. *Journal of Ethnopharmacology*. **86**: 197–202(2003).
57. G.V. Haslalka, C.R. Patil, M.R. Patil. Indian J. Pharmacol. 39(4): 201-205 (2007).
58. M. Dorr, D. Joycee, R.D. Porsolt, H. Steinberg, A. Summerfield, and M. Tomkiewiez. Persistence of dose-related behaviour in mice. *Nature*. **231**: 121-123 (1971).
59. J.M. Fujimoto, K.B. Peare, and G.L. Plaa. Barbiturate metabolism as affected by certain agents acting on the liver. *J. of Pharmacology and experimental Therapeutics*. **129**: 139-143 (1960).
60. H. Fujimori. Potentiation of barbital hypnosis as an evaluation method for CNS depressant. *Psychopharmacology*. **7**: 374-377 (1995).
61. H.P. Rang, M.M. Dale, and J.M. Ritter. Chemical transmisión and drug action in central nervous system, In Pharmacology 3rd ed. Churchill Livingstone. Edinburgh. 491-561 (1996).
62. S. Pal, T. Sen, and A.K.N. Chaudhuri. Neuropsychopharmacological profile of the methanolic fraction of *Bryophyllum Pinnatum* leaf extract. *Journal of Pharmacy and Pharmacology*. **51(3)**: 313-318 (1999).
63. L. Scrima, M. Broudy, K.N. Nay, and M.A. Cohn. Increased severity of obstructive sheep apnea after bedtime alcohol ingestation, diagnostic potential and proposed mechanism of action. *Sleep*. **5**: 318-328 (1982).
64. D.J. Radford, A.D. Gillies, and J.A. Hinds. Naturally occurring cardiac glycoside. *Med. J. Aust*. **144:** 540-544 (1986).
65. H.M. Salahdeen, and O.K. Yemitan. Neuropharmacological Effects of Aqueous Leaf Extract of *Bryophyllum Pinnatum* in Mice. *African Journal of Biomedical Research*. **9**: 101–107(2006).
66. O.K. Yemitan, and H.M. Salahdeen. Neurosedative and muscle relaxant activities of aqueous extract of *Bryophyllum pinnatum*. *Fitoterapia*. **76**: 187-193(2005).
67. E.E. Obaseiki-Ebor, K. Odukoya, H. Telikepalli, L.A. Mitscher, and D.M. Shankel. Antimutagenic activity of extracts of leaves of four common edible vegetable plants in Nigeria (west Africa). *Mutat. Res*. **302(2**): 109-117 (1993).
68. G. Umbuzeiro-Valent, D.A. Roubicek, and E.M. Haebisch. Mutagenic and Antimutagenic evaluation of the juice of the leaves of *Bryophyllum Calycinium*, A plant with Antihistamine activity. *Environ Mol. Mutagen*. **33(4)**:325-327 (1999).
69. C.Z. Nassis, E.M. Haebisch, and A.M. Giesbrecht. Antihistamine activity of *Bryophyllum Calycinum*. *Braz J. Med Bio. Res*. **25(9)**:929-936 (1992).
70. Chem Abstr. 105: 158797m (1986).
71. N. Salah, N.J. Miller, G. Pagange, L. Tijburg, G.P. Bolwell, E. Rice, and C. Evans. Polyphenolic flavonoids as scavenger of aqueous phase radicals as chain breaking antioxidant. *Arch Biochem. Broph*. **2**: 339-346 (1995).
72. A. Del-Rio, B.G. Obdululio, J. Casfillo, F.G. Marin, and A. Ortuno. Uses and properties of citrus flavonoids. *J. Agric Food Chem*. **45**: 4505-4515 (1997).
73. J.K. Adesanwo, Y. Raji, S.B. Olaleye, S.A. Onasanwo, O.O. Fadare, O.O. Ige, and O. O. Odusanya. Antiulcer Activity of Methanolic Extract of *Bryophyllum pinnatum* in Rats, *Journal of Biological Sciences*. 409-412.
74. D.E. Okwu. Evaluation of the chemical composition of indigenous spices of southeastern Nigeria. *Global J. Pure Appl. Sci*. **7**: 455-459 (2001).
75. K.C. Ofokansi, C.O. Esimone, and C.K. Anele. Evaluation of the in vitro combined antibacterial effect of the leaf extracts of *Bryophyllum pinnatum* (Fam: crassulaceae) and *Ocimum gratissimum* (Fam: labiatae). *Plant Prod. Res. J*. **9**: 23-27 (2005).
76. E.E. Obaseiki-Ebor. Preliminary report on the invitro antibacterial activity of *Bryophyllum pinnatum* leaf juice. *Afr J Med Med Sci*. **14(3-4)**:199-202 (1985).
77. A.C. Schmitt, A.B.P.F. Almeida, T.A. Silveira, C.T. Iwakura, K.F. Mendes, and M.C. Silva. Invitro antibacterial activity of *Bryophyllum pinnatum* ('Folha-da-fortuna') leaves from Varzea Grande, Mato Grosso/Brazil. *Acta Scientiae Veterinariae*. **31(1)**: 55-58 (2003).
78. J.C. Okaka, and A.N.O. Okaka. Food composition, Spoilage and shelf life extension. Ocjarco Academic Publishers, Enugu, Nig. 54-56 (2001).
79. J.A.O. Ojewole. Antinociceptive, anti-inflammatory and antidiabetic effects of *Bryophyllum pinnatum* (Crassulaceae) leaf aqueous extract. *Journal of Ethno pharmacology*. **99**: 13-19 (2005).
80. B. Rossi-Bergmann, S.S. Costa, M.B.S. Borges, S.A. da Silva, G.R. Noleto, M.L.M. Souza, and V.L.G. Moraes. Immunosuppresive effect of the aqueous extract of *Kalanchoe Pinnata* in mice. *Phytothera. Res*. **8:** 399-402 (1994).
81. B. Rossi-Bergmann, and S.S. Costa. Inhibition of Lymphocyte Activation by extracts by extracts and fractions of *Kalanchoe*, Alternathera, Paullinia and Mikania. *Phytomedicine*.**1(3)**: 199-204 (1994).
82. S.A. Igwe, and D.N. Akunyili. Analgesic Effects of Aqueous Extracts of the Leaves of *Bryophyllum pinnatum*. *Pharmaceutical Biology*. **43(8)**: 658 – 661 (2005).
83. L.K. Dahl. Salt and Hypertension. *Am. J. clin. Nutri*. **25**: 231-238 (1972).
84. M. Khan, P.A. Patil, and J.C. Shobha. Influence of *Bryophyllum pinnatum (Lam.*) leaf extract on wound healing in albino rats. *J. Natural Remedies*. **4**:41-46 (2004).
85. R.C. Agoha. Medicinal Plants of Nigeria. Offset Drakkerij. Faculfcitder Wiskunde in Naturwetenschappen, the Netherlands. 41, 33 (1974).
86. Dra. Amalia Dominguez Suarezy Tec. Maritza Bacallao. Actividad Antiinflamatoria de extracto fluido de hojas de siempreviva (*Bryophyllum Pinnatum*). *Rev Cubana Invest Biomed*. **21(2)**:86-90 (2002).
87. P. Siddharta, and A.K.N. Chaudhuri. Further studies on the Anti-inflammatory profile of the Methanolic Fraction of the fresh leaf extract of *Bryophyllum Pinnatum*. *Fitoterapia*. **63(5**): 451-459 (1992).
88. B. Gwehenberger, L. Rist, R. Huch, and U. von Mandach. Effect of *Bryophyllum pinnatum* versus fenoterol on uterine contractility. *Eur J Obstet Gynecol Reprod Biol*. **113(2)**:164-71 (2004).
89. N. Plangger, L. Rist, R. Zimmermann, and U.V. Mandach. Intravenous tocolysis with *Bryophyllum pinnatum* is better tolerated than

beta-agonist application. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. **124**: 168–172 (2006).

90. G.P. Reppas. *Bryophyllum Pinnatum* poisoning of Cattle. *Aust Vet J*. **72(11):** 425-427 (1995).
91. D.A. Alabi, I.A. Oyero, Jimoh and N.A. Amusa. Fungitoxic and Phytotoxic Effect of *Vernonia amygdalina (L), Bryophyllum pinnantus Kurz Ocimum gratissimum (Closium) L.* and *Eucalyptna globules (Caliptos) Labill* Water Extracts on Cowpea and Cowpea Seedling Pathogens in Ago-Iwoye, South Western Nigeria. *World Journal of Agricultural Sciences*. **1(1):** 70-75 (2005).
92. B.G. Sutton, and C.B. Osmond. Dark Fixation of CO2 by Crassulacean Plants Evidence for a single carboxylation step. *Plant Physiol*. **50**: 360-365 (1972).
93. U. Supratman, T. Fujita, K. Akiyama, H. Hayashi, A. Murakami, H. Sakal, K. Koshimizu, and H. Ohigashi. Anti-tumor promoting activity of Bufdienolides from *Kalanchoe Pinnata* and *K. Daigremontiana X Tubiflora*. *Biosci Biotechnol Biochem*. **65(4)**: 947-949 (2001).