European Journal of Medicinal Plants
4(1): 86-104, 2014

SCIENCEDOMAIN *international*
www.sciencedomain.org

Genus *Kalanchoe* (Crassulaceae): A Review of Its Ethnomedicinal, Botanical, Chemical and Pharmacological Properties

Rola Milad[1*], Sherweit El-Ahmady[1] and Abdel Nasser Singab[1]

[1]Department of Pharmacognosy, Faculty of Pharmacy, Ain Shams University, Abbassia, 11566-Cairo, Egypt.

Authors' contributions

Authors may use the following wordings for this section: This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Review Article

Received 8th July 2013
Accepted 28th September 2013
Published 24th October 2013

ABSTRACT

Genus *Kalanchoe* comprises hundred species. Different extracts of these *Kalanchoe* species have been widely used in traditional medicine. Recently it has been reported that *Kalanchoe* extracts possess various biological activities viz. antiviral, sedative, antiulcer, immunomodulatory, antileishmanial, CNS depressant, anti-inflammatory, thyroid peroxidase inhibitor, cytotoxic, hepatoprotective, antioxidant, analgesic, anticonvulsant, antimicrobial, inhibition of B cell development, cardiovascular, antihyperglycemic, acetylcholinesterase inhibition, insecticidal and larvicidal activities. Earlier studies on different Kalanchoe species 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: Kalanchoe; crassulaceae; cytotoxic; flavonoids; cardiac glycosides; triterpenes.

**Corresponding author: Email: rolamilad@pharma.asu.edu.eg;*

1. INTRODUCTION

Kalanchoe is a genus belonging to family Crassulaceae; closely related to Saxifragaceae from which it differs in the regular numerical plan, almost constantly separate ovaries and predominately fleshy habit. Family Crassulaceae is widely distributed for horticulture. *Kalanchoe* comprises hundred species that are native to tropical areas, Africa and Brazil [1, 2, 3, 4, 5]. Other names of genus *Kalanchoe* are *Bryophyllum* and *Cotyledon* [6]. Amongst which are species *K. pinnata* Lam.; *K. brasiliensis* Larranaga; *K. diagremontiana* R. Hamet; *K. spathulata* DC.; *K. gracilis* Hance; *K. streptantha* Baker; *K. blossfeldiana* Poelln.; *K. tubiflora* Raym. Hamet.; *K. angolensis* N. E. Br; *K. bentii* C. H. Wright; *K. diversa* N. E. Br; *K. dyeri* N. E. Br; *K. elizae* Berger; *K. felthamensis* Hort.; *K. kewensis* Hort; *K. latisepala* N. E. Br.; *K. luciae* Hamet; *K. magnidens* N. E. Br.; *K. prasina* N. E. Br.; *K. somaliensis* Baker; *K. sexangularis* N. E. Br.; *K. flammea* Stapf; *K. kirkii* N. E. Br.; *K. glaucescens* Birt.; *K. rotundifolia* Haw.; *K. carnea* Mast.; *K. laciniata* DC; *K. laxiflora* Baker*, K marmorata* Baker and *K. verticillata* Elliot; those are the most cited in literature [7,8].

2. ETHNOMEDICINAL OR TRADITIONAL USES

The juice of *Kalanchoe* is used for the local treatment of periodontal disease, cheilitis, cracking lips in children, bruises, wounds, boils in Brazil [9], insect bites in India and Srilanka [10], ear infection, dysentery in Nigeria [11], fever, abscesses, coughs, skin diseases and cytotoxic activity [12], cholera, urinary diseases, whitlow in Africa and Asia [13], tissue injuries in Taiwan [14], arthritis and gastric ulcers [10]. Crushed leaves are rubbed on or tied to the head to bring relief for headache in Africa [11], rheumatism in Indonesia [15], treatment of pulmonary infection, rheumatoid arthritis, immunomodulatory and gastric ulcers [16].

3. BOTANICAL DESCRIPTION

Family Crassulaceae or orpine family, stonecrop family, Synonym: Sedaceae, 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. 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 carpels [7].

The leaf usually centric or intermediate between dorsiventral and centric; typical palisade tissue rare, opposite, or alternate, exstipulate. Hairs are usually infrequent, but several kinds recorded; bladder-like hairs sometimes described as epidermal cells; glandular hairs with short or long stalks and which sometimes secrete mucilage; three armed, pointed hairs; biseriate hairs forming a cobweb-like surface to the leaf, together with transitions between these and glandular shaggy types. The leaf surface often covered by a bluish-white coating

of wax secreted from the epidermis. The epidermis is usually composed of cells elongated transversely to the longitudinal axis of the leaf; papillosed in a few species. 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 or only on the lower surface. Secretory cells, with apparently tanniniferous contents, common in unlignified 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 [7,17].

The stem is a fleshy structure due to the well developed parenchymatous or collenchymatous tissues of the cortex and pith. Cork usually consisting of thin-walled cells, arising in the epidermis but sometimes sub-epidermal or even more deeply seated in other genera as becoming impregnated with resin and forming a thick layer capable of reducing evaporation in certain species of *Kalanchoe* from Madagascar namely *K. crenata*. Cortex well developed, fleshy; consisting wholly of parenchyma or with the outer part collenchymatous. Centric, sometimes numerous cortical bundles with central xylem present in certain genera. Phloem poorly developed, including narrow sieve tubes which are not easily seen. Xylem nearly always in the form of a continuous cylinder, only rarely dissected by wide rays [7,17].

The root is described as having red root tips, colored by an anthocyan pigment which is intensified by bright light [7,17].

The flowers are bisexual, rarely unisexual then dioecious, actinomorphic, 3- 4- to 5- merous; sepals free or united into a tube, persistant; petals as many as the sepals, free or united; stamens hypogynous or epipetalous, as many as the petals or twice as many; filaments free or adnate to the petals; scale like nectaries usually present between the stamens and carpels. Carpels are superior, equal in number to the petals, free or slightly connate at the base, monolocular; numerous ovules; style is short or elongate [1]. The flowers are generally arranged in cymose inflorescences at the end of the leaf-shoot, or in lateral cymes. They form dichasia with a tendency to pass into monochasia, or are purely monochasial. Dichasia and monochasia may be arranged in racemes, corymbs, umbels or panicles [18]. The fruit is follicular; seeds are minute and elongated; embryo is straight and endosperm is present [1].

4. CHEMICAL PHYTOCONSTITUENTS

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

4.1. Flavonoid Glycosides

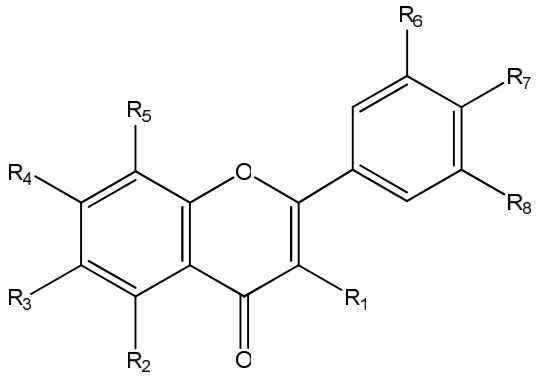
Published data concerning the isolation & structural elucidation of flavonoid glycosides [5, 14, 19, 20, 21, 22, 23, 24, 25, 26] from different organs of the aforementioned *Kalanchoe* species are summarized in Table 1 & 2.

Table 1. Flavonoids isolated from Genus *Kalanchoe*

Compound Name	Compound No.	Species	Part used	Reference
Patuletin-3,7-di-*O*-rhamnoside	**1**	*K. spathulata*	Leaves & flowers	[5]
Patuletin	**2**			
Quercetin	**3**			
Quercetin-3-*O*-glucoside-7-*O*- rhamnoside	**4**			
Kaempferol	**5**			
Kaempferol-3-*O*-rhamnoside	**6**			
Eupafolin-4'-*O*-rhamnoside	**7**	*K. gracilis*	Aerial parts	[14]
Eupafolin-3-7 di-*O*-rhamnoside	**8**			
Eupafolin-3-*O*-rhamnosyl-7-*O*-(4-*O*- acetylrhamnoside)	**9**			
Eupafolin-3-*O*-(3-*O*-acetylrhamnosyl)- 7-*O*-(3-*O*-acetylrhamnoside)	**10**			
Luteolin	**11**			
Quercetin	**3**			
Quercitrin	**12**			
Kaempferol	**5**			
Eupafolin	**13**			
Patuletin-3-*O*-(4''-*O*-acetyl-*α*-*L*- rhamnopyranosyl)-7-*O*-(2'''-*O*-acetyl-*α*- *L*-rhamnopyranoside)	**14**	*K. brasiliensis*	Juice of fresh stems & leaves	[19]
Patuletin-3-*O*-*α*-L-rhamnopyranosyl-7 *O*-(2'''-*O*-acetyl-*α*-*L*-rhamnopyranoside)	**15**			
Patuletin-3-*O*-(4''-*O*-acetyl-*α*-*L*-rhamnopyranosyl)-7-*O*-rhamnopyranoside	**16**			
4''''-acetylsagittatin A	**17**	*K. streptantha*	Leaves	[20]
Quercetin	**3**	*K. blossfeldiana*		[21]
Quercetrin	**12**			
Quercetin-3-*O*-*β*-*D*-glucoside	**18**			
Quercitrin	**12**	*K. pinnata*	Fresh leaves	[22]
Kapinnatoside	**19**			
Quercetin-3-*O*-α-*L*-arabinopyranosyl (1 → 2) *α*-*L*-rhamnopyranoside	**20**			

8-methoxyquercetin-3,7-di-*O*- rhamnopyranoside	**21**	*K. brasiliensis*, *K. pinnata* & *K. gastonis-bornieri*	Extracts	[23]
8-methoxykaempferol-3,7-di-*O*- rhamnopyranoside	**22**			
Isorhamnetin-3-O-α-L-$^{1}C_{4}$-rhamnopyranoside	**23**	*K. marmorata*	Leaves	[24]
Quercetin	**3**			
4'-methoxy-myricetin-3-O-α-L-$^{1}C_{4}$-rhamnopyranoside	**24**			
Quercitin -3-O-β-D-$^{4}C_{1}$-glucopyranoside	**18**			
Kaempferitrin	**25**	*Bryophyllum pinnatum*		[25]
Kaempferol 3-O-α-L-(2-acetyl)rhamnopyranoside-7-O-α-L-rhamnopyranoside	**26**			
Kaempferol 3-O-α-L-(3-acetyl)rhamnopyranoside-7-O-α-L-rhamnopyranoside	**27**			
Kaempferol 3-O-α-L-(4-acetyl)rhamnopyranoside-7-O-α-L-rhamnopyranoside	**28**			
Kaempferol 3-O-α-D-glucopyranoside-7-O-α-L-rhamnopyranoside	**29**			
Afzelin	**30**			
α-rhamnoisorobin	**31**			
3',4'-dimethoxy quercetin	**32**	*K. pinnata*	Leaves	[26]

Table 2. Chemical Structures of Flavonoids Isolated from Genus *Kalanchoe*



Compound #	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
1	O-rhamnoside	OH	OCH_3	O-rhamnoside	H	OH	OH	H
2	OH	OH	OCH_3	OH	H	OH	OH	H
3	OH	OH	H	OH	H	OH	OH	H
4	O-glucoside	OH	H	O-rhamnoside	H	OH	OH	H
5	OH	OH	H	OH	H	H	OH	H
6	O-rhamnoside	OH	H	OH	H	H	OH	H
7	OH	OH	OCH_3	OH	H	H	O-rhamnoside	H
8	O-rhamnoside	OH	OCH_3	O-rhamnoside	H	H	OH	H
9	O-rhamnoside	OH	OCH_3	4-O-acetyl rhamnoside	H	H	OH	H
10	3-O-acetyl rhamnoside	OH	OCH_3	3-O-acetyl rhamnoside	H	H	OH	H
11	H	OH	H	OH	H	OH	OH	H
12	O-rhamnoside	OH	H	OH	H	OH	OH	H
13	OH	OH	OCH_3	OH	H	H	OH	H
14	4"-O-acetyl rhamnoside	OH	OCH_3	2'"-O-acetyl rhamnoside	H	OH	OH	H
15	O-rhamnoside	OH	OCH_3	2'"-O-acetyl rhamnoside	H	OH	OH	H
16	4"-O-acetyl rhamnoside	OH	OCH_3	O-rhamnoside	H	OH	OH	H
17	O-xylose (1 2) rhamnoside	OH	H	O-acetyl rhamnoside	H	H	OH	H
18	O-glucoside	OH	H	OH	H	OH	OH	H
19	O-arabinoside (1 2) rhamnoside	OH	H	OH	H	H	OH	H
20	O-arabinoside (1 2) rhamnoside	OH	H	OH	H	OH	OH	H
21	O-rhamnoside	OH	H	O-rhamnoside	OCH_3	OH	OH	H
22	O-rhamnoside	OH	H	O-rhamnoside	OCH_3	H	OH	H
23	O-rhamnoside	OH	H	OH	H	OCH_3	OH	H
24	O-rhamnoside	OH	H	OH	H	OH	OCH_3	OH
25	O-rhamnoside	OH	H	O-rhamnoside	H	H	OH	H
26	O-2 acetyl rhamnoside	OH	H	O-rhamnoside	H	H	OH	H
27	O-3 acetyl rhamnoside	OH	H	O-rhamnoside	H	H	OH	H
28	O-4 acetyl rhamnoside	OH	H	O-rhamnoside	H	H	OH	H
29	O-glucoside	OH	H	O-rhamnoside	H	H	OH	H
30	O-rhamnoside	OH	H	OH	H	H	OH	H
31	OH	OH	H	O-rhamnoside	H	H	OH	H
32	OH	OH	H	OH	H	OCH_3	OCH_3	H

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 [21].

4.3 Coumarins

5-hydroxycoumarin was isolated from the aerial parts of *K. gracilis* [14].

4.4 Bufadienolides

Genus *Kalanchoe* is reported to contain plant cytotoxic bufadienolides [12, 15, 27,28,29,30, 31]. The isolated bufadienolides from leaves and whole aerial parts from different *Kalanchoe* species are reported in Table 3, Figure 1.

Table 3. Bufadienolides isolated from Genus *Kalanchoe*

Compound Name	Compound #	Species	Part used	Reference
Hellibrigenin-3-acetate	**33**	*K. lanceolata*	Leaves	[27]
Bersaldegenin-1,3,5-orthoacetate	**34**	*K. daigremontiana* *K. tubiflora*	Leaves	[28]
Daigremontianin	**35**			
Bryophyllin B	**36**	*Bryophyllum pinnatum*	Leaves	[29]
Bryophyllin A (Bryotoxic C)	**37**	*K. pinnata*	Leaves	[30]
Bryophyllin C	**38**	*K. daigremontiana* ×*tubiflora*	Leaves	[15]
Bersaldegenin-1,3,5-orthoacetate	**34**			
Bryophyllin A	**37**			
Bryophyllin C	**38**			
Daigremontianin	**35**			
Methyl Daigremonate	**39**			
Bersaldegenin-3-orthoacetate	**40**			
Bersaldegenin-1-orthoacetate	**41**			
Kalanchoside A	**42**	*K. gracilis*	Aerial parts	[31]
Kalanchoside B	**43**			
Kalanchoside C	**44**			
Kalanhybrin A	**45**	*K. hybrida*	Whole plant	[12]
Kalanhybrin B	**46**			
Kalanhybrin C	**47**			
Daigredorigenin-3-acetate	**48**			

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* [12]. Protocatechuic-4'-O-β-D-$^4C_1$-glucopyranoside was isolated from the ethyl acetate fraction of the leaf aqueous extract of *K. marmorata* [24]. Blumenol A, a megstigmane derivative, was isolated from the methanol extracts of *K. hybrida* [12].

4.6 Sterols, Triterpenes and Phenanthrenes

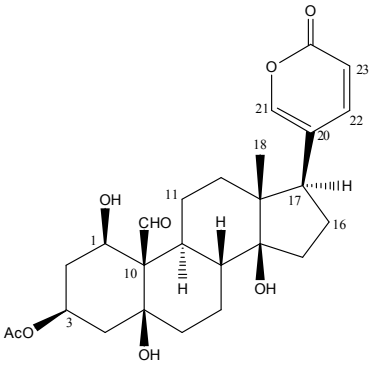
Several compounds had been isolated from the fresh leaves of *Bryophyllum pinnatum*, namely bryophyllol, bryophollone and bryophollenone, bryophynol and 18*α*- oleanane, *ψ*-taraxasterol, along with a mixture of *α*- and *β*-amyrins and their acetates [13] and from the whole aerial parts 5*α*- stigmast- 24-en-3*β*-ol; 25-methyl- 5*α*-ergost-24 (28)- en-3*β*–ol; (24*R*)-stigmasta- 5, 25- dien- 3*β*-ol (24-epiclerosterol) and (24*R*)- 5*α*- stigmasta- 7, 25-dien-3*β*-ol were isolated [32]. On the other hand, 3-oxo-olean-12-ene and *β*-sitosterol had isolated from the dichloromethane fraction of the leaves of *K. thrysiflora* [33].

4.7 Organic Salts

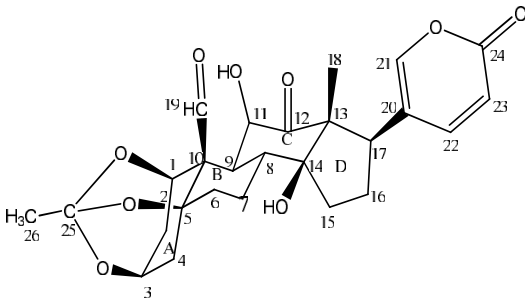
Kalanchosine dimalate (KMC) is an anti-inflammatory salt from the fresh juice of the aerial parts of *Kalanchoe brasiliensis* [34].

4.8 Fatty Acids

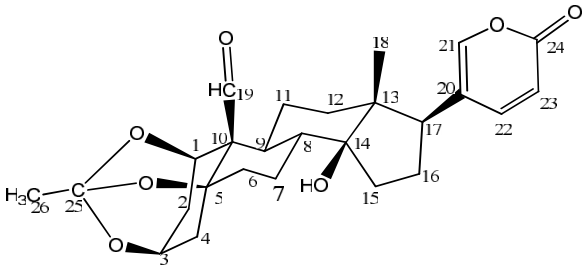
Palmitic acid (C16), stearic acid (C18) and traces of arachidic (C20) and behenic acids (C22) were identified from the ethanol extract of *Kalanchoe pinnata* [35].



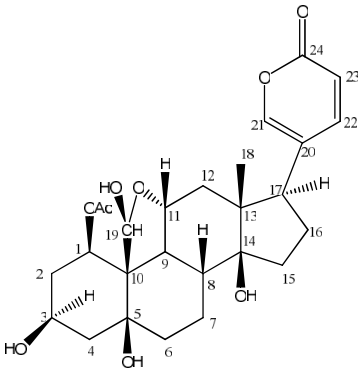
Hellibrigenin-3-acetate 33



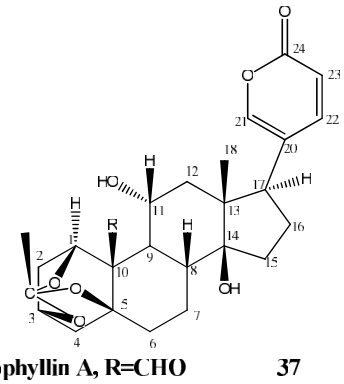
Daigremontianin 35



Bersaldegenin-1, 3, 5-orthoacetate 34

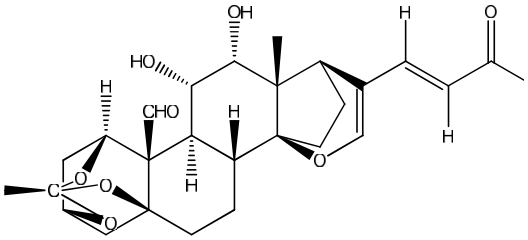


Bryophyllin B 36

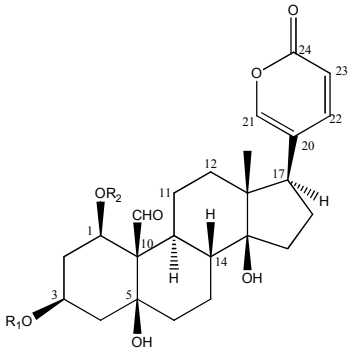


Bryophyllin A, R=CHO 37

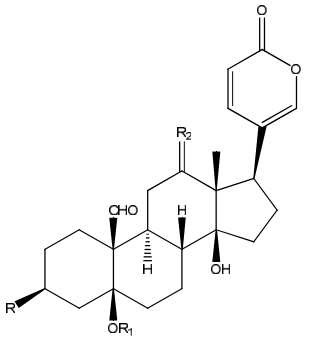
Bryophyllin C, R=CH_2OH 38

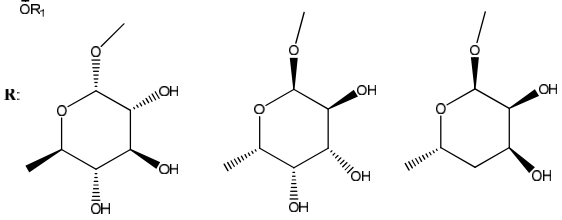


Methyl diagremonate **39**



Bersaldegenin-3-acetate, R_1=Ac; R_2=H **40**
Bersaldegenin-1-acetate, R_1=H; R_2=Ac **41**





R:			
R_1	H	H	H
R_2	H_2	H_2	O

Kalanchoside A **42**
Kalanchoside B **43**
Kalanchoside C **44**

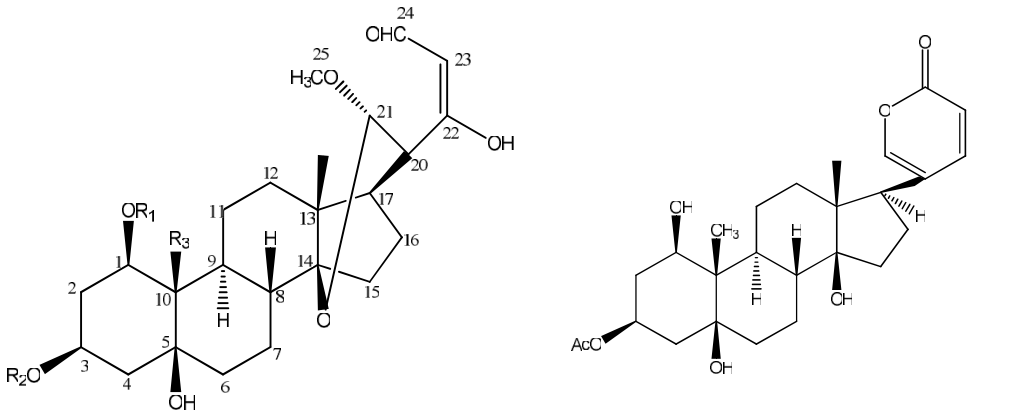


Fig. 1. Structure of Bufadienolides isolated from Genus *Kalanchoe*

5. PHARMACOLOGICAL PROPERTIES

A review of literature revealed that genus *Kalanchoe* had several pharmacological activities viz antiviral, sedative, antiulcer, immunomodulatory, antilieshmanial, CNS depressant, anti-inflammatory, 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 [28].

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 pre-treated 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 [10]. The fractionation of the juice of the fresh stems and leaves of *K. brasiliensis* was monitored by an assay measuring lymphocyte proliferation [19]. Recently, the protective effect of the leaves of *K. pinnata* in fatal anaphylactic shock, likewise a Th2 type T cell-driven immunopathology were 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[16].

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 [22, 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 behavior pattern, caused dose-dependent potentiation of pentobarbitone sleeping time and had significant analgesic activity. On the other side reduction of exploratory behavior 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 [34].

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 [29]. 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 [31]. 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 [12]**.** 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 were 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 [33].

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 CCl_4-induced hepatotoxicity model. The test material was found effective as hepatoprotective as evidenced by *in-vi*tro, *in-vivo* and histopathological studies. The juice was found more effective than ethanol extract [45].

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 [46].

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 [47]. 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 [48].

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 [48].

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 albica*ns were found to resist the action of the test extract [11]. 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 [49]. The antibacterial activity of the methanol extract of *K. farinace* was demonstrated against Gram-positive bacteria including multiresistant *Staphylococcus* strains [50]. 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 [51]. 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 [52].

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 [53].

5.16 Cardiovascular Effects

The effects of the *n*-butanol extract from the leaves of *K. crenata* was 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 [54].

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 [55].

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* [23].

5.19 Insecticidal and Larvicidal Activity

The methanol extract of the leaves of *K. pinnata* [30] 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 [15]. The extracts of *K. brasiliensis*, *K. pinnata* and *K. gastonis-bornieri* showed a toxic effect on *Aedes aegypti larvae* [23].

5. 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 [6].

6. 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 [33].

7. 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.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Boulos L. Flora of Egypt (1), Al Hadara Publishing, Cairo, Egypt; 1999.
2. Lawrence GHM. Taxonomy of Vascular Plants. The Macmillan Company, New York, 1958.
3. Trease GE, Evans WC. Textbook of Pharmacognosy 16th edition, Tyndall and Cassel, London; 2009.
4. Chopra RN, Nayar SL, Chopra IC. Glossary of Indian medicinal products. The Council for Scientific and Industrial Research. New Delhi; 1956.
5. Gaind KN, Singla AK, Wallace JW. Flavonoid glycoside of *Kalanchoe spathulata*. Phytochemistry. 1981;20:530-531.
6. Maurice M. Handbook of African Medicinal Plant. CRC press, Boca Raton, Ann Arbor, London, Tokyo; 1993.
7. Bailey LH. The standard Cyclopedia of Horticulture (1&2), The Macmillan Company, New York; 1953.
8. Bailey LH. The standard Cyclopedia of Horticulture (1&2), The Macmillan Company, New York, 1958.
9. Mourao RHV, Santos FO, Franzotti EM, Moreno MPN, Antoniolli AR. Anti-inflammatory activity and acute toxicity (LD_{50}) of the juice of *Kalanchoe brasiliensis* comb. leaves picked before and during blooming. Phytotherapy Research. 1999;13:352-354.

10. Rossi-Bergmann B, Costa SS, Borges MBS, Da Silva SA, Noleto GR, Souza MLM, Moraes VLG. Immunosuppressive effect of the aqueous extract of *Kalanchoe pinnata* in mice. Phytotherapy Research. 1994;8:399-402.
11. Akinpelu DA. Antimicrobial activity of *Bryophyllum pinnatum* leaves. Fitoterapia. 2000;71:193-194.
12. Kuo PC, Kuo TH, Su CR, Liou MJ, Wu TS. Cytotoxic principles and *α*-pyrone ring-opening derivatives of bufadienolides from *Kalanchoe hybrida*. Tetrahedron. 2008;64:3392- 3396.
13. Siddiqui S, Faizi S, Siddiqui BS, Sultana N. Triterpenoids and phenanthrenes from leaves of *Bryophyllum Pinnatum.* Phytochemistry. 1989; 28: 2433-2438.
14. Liu KCS, Yang SL, Roberts MF, Phillipson JD. Eupafolin rhamnosides from *Kalanchoe gracilis*. Journal of Natural Products. 1989; 52: 970-974.
15. Supratman U, Fujita T, Akiyama K, Hayashi H. Insecticidal compounds from *Kalanchoe daigremontiana* × *tubiflora*. Phytochemistry. 2001; 58: 311–314.
16. Cruz EA, Da-Silva SAG, Muzitano MF, Silva PMR, Costa SS, Rossi-Bergmann B. Immunomodulatory pretreatment with *Kalanchoe pinnata* extract and its quercitrin flavonoid effectively protects mice against fatal anaphylactic shock. International Immunopharmacology. 2008;8:1616–1621.
17. Metcalef CR, Chalk L. Anatomy of the Dicotyledons I. Oxford at the Clarendon Press; 1950.
18. Rendle AB. The classification of Flowering Plants 2 Cambridge at the University Press; 1959.
19. Costa SS, Jossang A, Bodo B. Patuletin acetylrhamnosides from *Kalanchoe brasiliensis* as inhibitors of human lymphocyte proliferative activity. Journal of Natural Products. 1994;57(11):1503-1510.
20. Costa SS, Jossang A, Bodo B. 4""- Acetylsagittatin A, a kaempferol triglycoside from *Kalanchoe streptantha.* Journal of Natural Product. 1996; 59:327-329.
21. Nielsen AH, Olsen CE, Moller BL. Flavonoids in flowers of 16 *Kalanchoe blossfeldiana* varieties. Phytochemistry. 2005;66:2829–2835.
22. Muzitano, MF, Cruz EA, De almedia AP, Da Silva SAG, Kaiser CR, Guette C, Rosibergmann B, Costa SS. Quercitrin: An antileishmanial flavonoid glycoside from *Kalanchoe pinnata.* Planta medica. 2006;72:81-83.
23. Trevisan MTS, Bezerra MZB, Santiago GMP, Feitosa CM, Verpoorte R, Braz R. Larvicides and acetyl-cholinesterase inhibitors from *Kalanchoe* species. Quimica Nova. 2006;29:415-418.
24. Singab AB, El-Ahamdy SH, Labib RM, Fekry SS. Phenolics from *Kalanchoe marmorata* Baker, family Crassulaceae. Bulletin of Faculty of Pharmacy, Cairo University. 2011;49:1–5.
25. Tatsimo SJN, Tamokou JD, Havyarimana L, Csupor D, Forgo P, Hohmann J, Kuiate JR and Tane P. Antimicrobial and antioxidant activity of Kaempferol rhamnoside derivatives from *Bryophyllum pinnatum*. BMC Research Notes 2012, 5:158
26. Megawati AK, Fajriah S. 3',4'-Dimethoxy Quercetin, a Flavonol Compound Isolated from *Kalanchoe pinnata.* Journal of Applied Pharmaceutical Science. 2013; 3 (01), 088-090.
27. Anderson LA, Schultz RA, Joubert JP, Prozesky L, Kellerman TS, Erasmus GL, Procos J. Krimpsiekte and acute cardiac glycoside poisoning in sheep caused by bufadienolides from the plant *Kalanchoe lanceolata* Forsk. Onderstepoort. Journal Veterinary Research. 1983;50(4):295-300.
28. Wagner H, Fischer M, Lotter H. Isolation and structure determination of daigremontianin, a novel bufadienolide from *Kalanchoe daigremontiana*. Planta Medica. 1985;169–170.

29. Yamagishi T, Haruna M, Yan XZ, Chang JJ, Lee KH. Antitumor agents, Bryophyllin B, A novel potent cytotoxic bufadienolide from *Bryophyllum pinnatum*. Journal of Natural Products. 1989;52(5):1071-1079.
30. Supratman U, Fujita T, Akiyama K, Hayashi H. New insecticidal Bufadienolide, Bryophyllin C, from *Kalanchoe pinnata*. Bioscience Biotechnology Biochemistry. 2000;64(6):1310-1312.
31. Wu PL, Hsu YL, Wu TS, Bastow KF, Lee KH. Kalanchosides A-C, new cytotoxic bufadienolides from the aerial parts of *Kalanchoe gracilis.* Organic Letters. 2006;8:5207-5210.
32. Akishia T, Kokke WCMC, Tamura T, Matsumoto T. Sterols of *Kalanchoe pinnata*. First report of the isolation of both C-24 epimers of 24-Alkyl-Δ^{25}-sterol from higher plants. Lipids. 1991;26:660–665.
33. Singab AB, El-Ahamdy SH, Labib RM, Fekry SS. *Kalanchoe thrysiflora* Harv. and *Kalanchoe marmorata* Baker; DNA Profiling, biological guided fractionation of different extracts; isolation and identification of cytotoxic compounds. Journal of Applied Pharmaceutical Science. 2012;02 (08):215-220
34. Costa SS, Souza MM, Ibrahim T, Melo GO, Almeida AP, Guette C, Ferezou JP, Koatz VLG. Kalanchosine dimalate, an anti-inflammatory salt from *Kalanchoe brasiliensis*. Journal of Natural Products. 2006; 69: 815-818.
35. Almeida AP, Da Silva AG, Souza MLM, Lima LMTR, Rossi Bergmann B, Goncalves de Moraes VL, Costa SS. Isolation and chemical analysis of a fatty acid fraction of *Kalanchoe pinnata* with a potent lymphocyte suppressive activity. Planta Medica. 2000; 66:134-137.
36. Shirobokov VP, Evtushenko AI, Lapchik VF, Shirobokov DN, Suptel EA. Antiviral activity of representatives of the family Crassulaceae. Antibiotiki. 1981; 26 (12): 897-900.
37. Pal S, Nag Chaudhuri AK. Studies on the antiulcer activity of *Bryophyllum pinnatum* leaf extract in experimental animals. Journal of Ethnopharmacology. 1991; 33: 97–102.
38. Da Silva SAG, Costa SS, Mendonca SCF, Silva EM, Moraes VLG, Rossi-Bergmann B. Therapeutic effect of oral *Kalanchoe pinnata* leaf extract in murine leishmaniasis. Acta Tropica. 1995; 60: 201-210.
39. Muzitano MF, Tinoco LW, Guette C, Kaiser CR, Rossi- Bergmann B, Costa SS. The antileishmanial activity assessment of unusual flavonoids from *Kalanchoe pinnata*. Phytochemistry. 2006; 67: 2071–2077.
40. Muzitano MF, Falcão CA, Cruz EA, Bergonzi MC, Bilia AR, Vincieri FF, Rossi-Bergmann B, Costa SS. Oral metabolism and efficacy of *Kalanchoe pinnata* flavonoids in a murine model of cutaneous leishmaniasis. Planta Medica. 2009; 75(4): 307-11.
41. Pal S, Sen T, Nag Chaudhuri AK. Neuropsychopharmacological profile of the methanolic fraction of *Bryophyllum pinnatum* leaf extract. Journal of Pharmacy and Pharmacology. 1999; 51: 313-318.
42. Ibrahim T, Cunha JMT, Madi K, Da Fonseca LMB, Costa SS, Koatz VLGA. Immunomodulatory and anti-inflammatory effects of *Kalanchoe brasiliensis*. International Immunopharmacology. 2002; 2: 875–883.
43. Ferreira AAF, Rosenthal D, Carvalho DP. Thyroid peroxidase inhibition by *Kalanchoe brasiliensis* aqueous extract. Food *and Chemical Toxicolog*y. 2000; 38: 417-421.
44. Supratman U, Fujita T, Akiyama K, Hayashi H, Murakami A, Sakai H, Koshimizu K, Ohigashi H. Anti-tumor promoting activity of bufadienolides from *Kalanchoe pinnata* and *Kalanchoe daigremontiana* × *tubiflora.* Bioscience Biotechnology Biochemistry. 2001; 65(4): 947-949.

45. Yadav NP, Dixit VK. Hepatoprotective activity of leaves of *Kalanchoe pinnata* Pers. Journal of Ethnopharmacology. 2003; 86: 197–202.
46. Harlalka GV, Patil CR, Patil MR. Protective effect of *Kalanchoe pinnata* pers. (Crassulaceae) on gentamicin-induced nephrotoxicity in rats. Indian Journal of Pharmacology. 2007; 39: 201-205.
47. Nguelefack TB, Fotio AL, Wetcho P, Wansi SL, Dimo T, Kamanyi A. Analgesic properties of the aqueous and ethanol extracts of the leaves of *Kalanchoe crenata* (Crassulaceae). Phytotherapy Research. 2004; 18: 385-388.
48. Nguelefack TB, Nana P, Atsamo AD, Dimo T, Watcho P, Dongmo AB, Tapondjou LA, Njamen D, Wansi SL, Kamanyi A. Analgesic and anticonvulsant effects of extracts from the leaves of *Kalanchoe crenata* Andrews Haworth (Crassulaceae). Journal of Ethnopharmacology. 2006; 106: 70–75.
49. Tadeg H, Mohammed E, Asres K, Gebre-Mariam T. Antimicrobial activities of some selected traditional Ethiopian medicinal plants used in the treatment of skin disorders. Journal of Ethnopharmacology. 2005; 100: 168–17.
50. Monthana RAA, Lindequist U. Antimicrobial activity of some medicinal plants of the island Soqotra. Journal of Ethnopharmacology. 2005; 96: 177–181.
51. Akinsulire OR, Aibinu IE, Adenipekun T, Adelowotan T, Odugbemi T. *In vitro* antimicrobial activity of crude extracts from plants *Bryophyllum pinnatum* and *Kalanchoe crenata*. African Journal of Traditional Complementary and Alternative Medicines. 2007; 4: 338-344.
52. Nahar K, Khan MGU, Rahman MS, Begum B, Rashid MA. Antimicrobial and cytotoxic activities of *Bryophyllum daigremontianum*. Dhaka University, Journal Pharmacological Science. 2008; 7(1): 99-101.
53. Paiva LS, Hayashi EA, De Melo GO, Costa SS, Koatz VLG, Nobrega A. Inhibition of B cell development by kalanchosine dimalate. International Immunopharmacology. 2008; 8: 828–835.
54. Nguelefack TB, Dimo T, Dongmo AB, Sontia B, Fotio AL, Watcho P, Kamanyi A, Vierling W. Cardiovascular effects of the *n*-butanol extract from *Kalanchoe Crenata* leaves. Pharmaceutical Biology. 2008; 46: 846-853.
55. Kamgang R, Mboumi RY, Fondjo AF, Tagne MAF, Mengue N'dille GPR, Yonkeu J N. Antihyperglycaemic potential of the water-ethanol extract of *Kalanchoe crenata* (Crassulaceae). Journal of Natural Medicines. 2008;62:34-40.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=281&id=13&aid=2372