Revista Brasileira de Farmacognosia 29 (2019) 529–558

Brazilian Journal of Pharmacognosy
REVISTA BRASILEIRA DE FARMACOGNOSIA
www.elsevier.com/locate/bjp

Review

Kalanchoe laciniata and *Bryophyllum pinnatum*: an updated review about ethnopharmacology, phytochemistry, pharmacology and toxicology

Júlia M. Fernandes [a], Lorena M. Cunha [a], Eduardo Pereira Azevedo [c], Estela M.G. Lourenço [a], Matheus F. Fernandes-Pedrosa [b], Silvana M. Zucolotto [a,*]

[a] *Laboratório de Farmacognosia, Departamento de Farmácia, Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil*
[b] *Laboratório de Tecnologia e Biotecnologia Farmacêutica, Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil*
[c] *Laboratório de Farmacotécnica, Departamento de Farmácia, Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil*

ARTICLE INFO

Article history:
Received 19 September 2018
Accepted 30 January 2019
Available online 7 June 2019

Keywords:
Comparison
Flavonoid
Traditional use
Phytochemical
Pharmacology
Toxicology

ABSTRACT

The species *Kalanchoe laciniata* (L.) DC. and *Bryophyllum pinnatum* (Lam) Pers. are native from Brazil and Madagascar, respectively. Both belonging to the Crassulaceae family and being widely used by population as a natural anti-inflammatory agent. These species have similar leaf morphology and for this reason, they are known by the same popular name as "*saião*" or "*coirama*". Several studies have been published involving different parts and preparations of these species. Therefore, this review aims to provide an update overview about the traditional uses, chemical constitution, pharmacology and toxicology of *K. laciniata* and *B. pinnatum* species. An extensive literature review was conducted in different scientific databases. Various chemical constituents have been identified in extracts from different parts of *K. laciniata* and *B. pinnatum*, being flavonoids the major compounds. They have been traditionally used to treat inflammation, microbial infection, pain, respiratory diseases, gastritis, ulcers, diabetes and cancer tumors. Non-clinical *in vitro* assays evaluated mainly the antimicrobial and antioxidant activities, while *in vivo* assays evaluated the leishmanicide, anti-inflammatory and immunomodulatory activities. Regarding toxicity, few studies have been conducted for the two species. The information reported in this work might contribute to the recognition of the importance of *K. laciniata* and *B. pinnatum* species, as well as to direct further studies.

Introduction

The Crassulaceae family comprises approximately 33 genera and 1500 species distributed worldwide, except for Australia and the Pacific Islands (Allorge-Boiteau, 1996). This family presents xeromorphic characteristics that allows its species to adapt to bright light and water scarcity (Herrera, 2008). It has an important role on the research of biochemical, ecophysiological and phylogenetic aspects related to the Crassulacean Acid Metabolism (CAM), which is an evolutive adaptation of the pathway of photosynthetic carbon assimilation (Osmond, 1978). Among species, *Kalanchoe laciniata* (L.) DC. is native from Brazil and *Bryophyllum pinnatum* (Lam) Pers. from Madagascar (Allorge-Boiteau, 1996; Gehrig et al., 2001). Even though these plants are naturalized in Brazil, they are not endemic (Zappi, 2015).

Kalanchoe laciniata and *B. pinnatum* are both popularly known as "saião" or "coirama" and have been used to treat inflammatory disorders (Amaral et al., 2005). Due to the various ethnopharmacological reports attributed to these species, several research groups have conducted studies to prove their pharmacological or biological properties. In addition, some researchers have carried out phytochemical studies resulting in the identification of different classes of secondary metabolites, as well as the isolation of various constituents, specially from their leaves and aerial parts. Therefore, this review aims to provide an updated overview about the traditional uses, chemical constitution as well as pharmacological and

* Corresponding author.
E-mail: silvanazucolotto@ufrnnet.br (S.M. Zucolotto).

https://doi.org/10.1016/j.bjp.2019.01.012

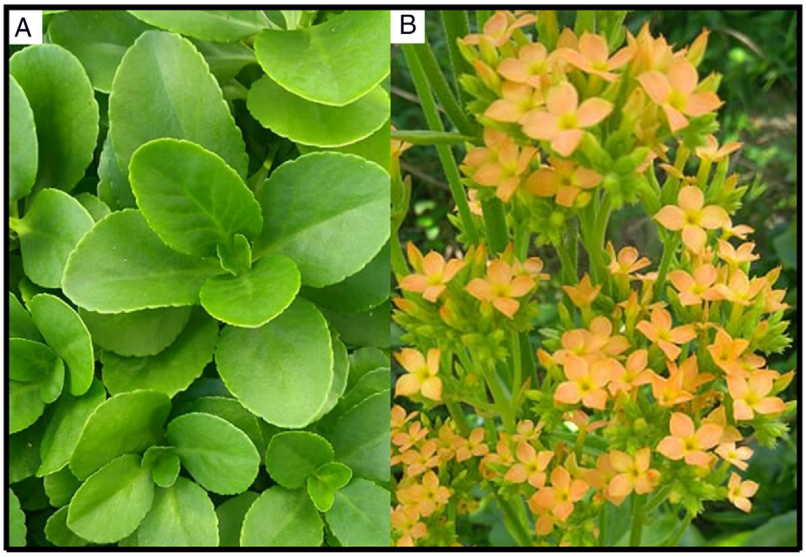


Fig. 1. Leaves (A) and inflorescences (B) of *Kalanchoe laciniata* (L.) DC.

toxicological aspects of *K. laciniata* and *B. pinnatum* species. This study might be used as a guide to further investigations involving these species.

Material and methods

An extensive literature review was conducted in different scientific databases such as PubMed, Web of Science, Scopus, Scielo, The Cochrane Library. The study covered several aspects of the vegetal species like botany, phytochemistry, traditional uses, pharmacology and toxicology. In addition, the scientific names, synonyms and popular names of major species identified by the botanical databases "Flora do Brasil", Tropicos, International Plant Names Index and The Plant List were included. The common names found in the book "Coletânea científica de plantas de uso medicinal" (Amaral et al., 2005) were also used. The data were updated in April 2018.

Botanical information

Kalanchoe laciniata and *Bryophyllum pinnatum* exhibit similarities concerning their leaf morphologies, which include decussate, succulent, glabrous, oval to elliptical leaves with crenate border (Hyakutake and Grotta, 1972; Anjoo and Saluja, 2010; Moreira et al., 2012). Due to such similarities, these species are known by the same popular name (Moreira et al., 2012). The knowledge of leaf anatomy is important for registration purpose and for quality control of herbal medicines (Moreira et al., 2012; Anvisa, 2014).

The *K. laciniata* (L.) DC. specie (Fig. 1) is popularly known as "saião", "corama-branca", "folha-da-fortuna", "para-tudo", "fortuna-de-flores-amarelas", "folha-da-costa", "folha-grossa" in Alagoas, "coerana" in Pernambuco, and "erva-da-costa" in Bahia. This species is found in almost all states of the Northeast region (Rio Grande do Norte, Ceará, Pernambuco, Paraíba, Bahia and Sergipe), Southeast (Espírito Santo, Rio de Janeiro, Minas Gerais and São Paulo), South (Paraná and Santa Catarina), Midwest (Federal District and Mato Grosso do Sul) and North (Acre) regions, mainly in the coastal zone (Allorge-Boiteau, 1996; Amaral et al., 2005; Zappi, 2015). The accepted name for this specie is *K. laciniata* (L.) DC. and others botanics synonyms are *Kalanchoe brasiliensis* and *Kalanchoe crenata* (The Plant List, 2010; Zappi, 2015; Tropicos, 2019). Although *K. laciniata* is the accepted name, most of the works found use its synonym of *K. brasiliensis*.

Kalanchoe laciniata constitutes a subligneous and perennial vegetable with 30–100 cm in height. Its leaves are succulent, oval or obval, opposites, shortly petiolate and crenate (Corrêa, 1984; Barroso, 1991; Amaral et al., 2005). The flowers are yellow-orange in collor, small, abundant, arranged in composite summits of stamps or paniculate, hermaphrodites, gamopetalas with corolla longer than the cup, with the presence of scaly carpels that become polispermos follicles. Their fruit is a follicle with 6 cm long that contains brown oblong seeds (Lorenzi and Matos, 2000; Amaral et al., 2005).

The *Bryophyllum pinnatum* (Lam) Pers. species (Fig. 2) is popularly known as "saião" and "coirama" throughout Brazil; "folha-de-pirarucu", in Pará State; "fortuna" and "roda-da-fortuna" in Minas Gerais; "zakham-hayat" in Asia and Africa; life-plant in Mexico; love-plant, canterburry, bells and cathedral bells in the United States of America and Europe (Amaral et al., 2005; Joseph et al., 2011). This species is found in Brazil, China, India and Africa and in all tropical countries. In Brazil, it is found in Northeast (Bahia, Ceará and Paraíba), North (Acre), Southeast (Espírito Santo, Rio de Janeiro, Minas Gerais and São Paulo), Midwest (Distrito Federal, Mato Grosso do Sul and Mato Grosso) and South (Paraná, Rio Grande do Sul and Santa Catarina) regions, mainly in the coastal and *Caatinga* zones (Amaral et al., 2005; Zappi, 2015). *B. pinnatum* (Lam) Pers. is the accepted name and *B. calycinum* and *Kalanchoe pinnata* are its botanic synonyms (The Plant List, 2010; Zappi, 2015; Tropicos, 2019).

Bryophyllum pinnatum is a perennial, succulent and corpulent vegetable with glabrous and tuberous stem. This species can reach up to 150 cm in height. The oldest stalks have a light color while the youngest ones are reddish with defilements. Its leaves are variable and decussates, being the lowest ones generally simple or sometimes imparinates. The leaves are 30 cm long, the upper are 3-5-7 foliated, long petiolate, thick, fleshy and dark with crenate borders. The inflorescences are hermaphrodites, tubular, pendulous, monopetalas, pale green or yellow-red, with cup swollen and corolla longer than the cup. The fruit are in the form of hoods which become scaly polispermos follicles that are housed within the hoods (Amaral et al., 2005; Jessica, 2008; Joseph et al., 2011; Moreira et al., 2012).

The main characteristic that differentiates *K. laciniata* and *B. pinnatum* species is the leaf aspect as *K. laciniata* has a corrugated or subcrenated border (Fig. 3), whereas *B. pinnatum* leaf is significantly crenate (Lorenzi and Matos, 2000).

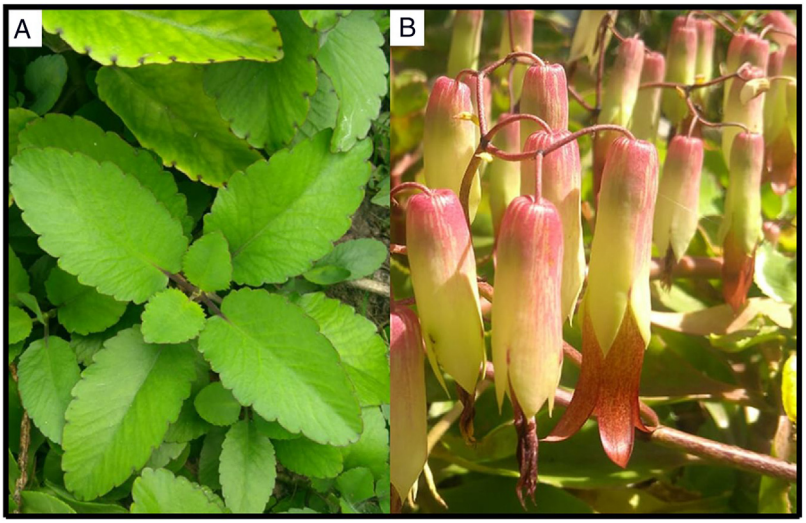


Fig. 2. Leaves (A) and inflorescences (B) of *Bryophyllum pinnatum* (Lam) Pers.

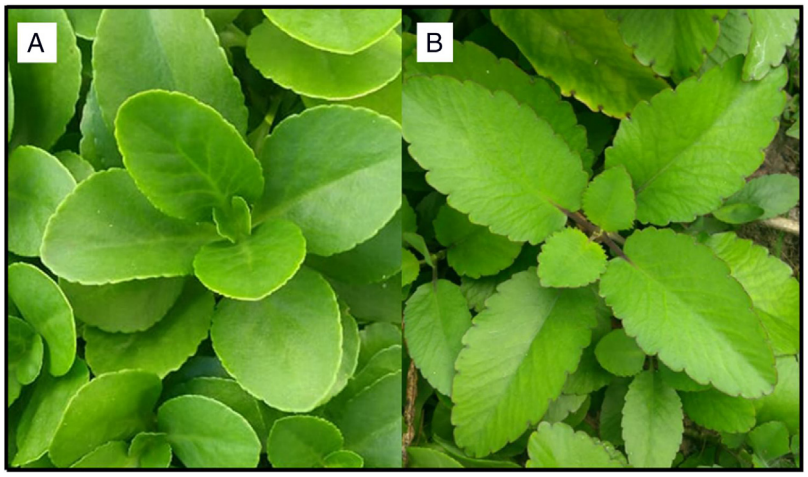


Fig. 3. Leaves of *Kalanchoe laciniata* (A) and *Bryophyllum pinnatum* (B).

Chemical constituents

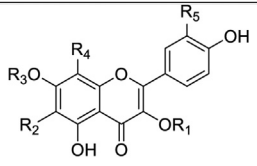
Various chemical constituents for *K. laciniata* and *B. pinnatum* have been reported in the literature, where they have been isolated mainly from the leaves of both species. The aqueous and methanolic are the most commonly used extracts of *K. laciniata* and *B. pinnatum*, respectively. Among the constituents that have been identified so far, flavonoids represent the class of secondary metabolites most commonly found, being the major component in both species. However, for *K. laciniata*, some patuletin aglycone derivatives have been identified, whereas for *B. pinnatum*, quercetin, kaempferol and luteolin aglucons were found. In addition, chlorophylls, carotenoids and polysaccharides have been identified for *K. laciniata*.

Despite the widespread use of *K. laciniata* and *B. pinnatum* by folk medicine practitioners, their chemical constituents have not been fully elucidated. Moreover, only few studies involved the isolation and elucidation of their chemical constituents, where the majority of the studies indicates the presence of glycosylated flavonoids, derived from the acetylation of the rhamnose ring of patuletin in different positions. The acetylation occurs at the end of the biosynthetic route of flavonoids, usually through esterifications of the hydroxyl groups (Aguiar et al., 2007). Flavonoids derived from patuletin have already been described for another species of the genus, *K. spathulata* (Gaind et al., 1981). Acetylated rhamnose flavonoids have been described for *B. pinnatum* but derived from canferol (Tatsimo et al., 2012). However, a quick search in the literature reveals that acetylated rhamnoses of patuletin have only been described for *K. laciniata* and *K. gracilis* by Costa et al. (1994) and Liu et al. (1989), respectively. Thus, these compounds are considered as potential candidates for specific markers of these species by presenting themselves as differentiators in relation to most other species, especially *B. pinnatum*. It is worth pointing out that until the date of this publication, no study have been published about the description of the bioactive compounds for this specie as only two studies were conducted by bioassay-guided isolation by Costa et al. (1994) and Trevisan et al. (2006). Box 1 summarizes the main compounds already described for *K. laciniata*.

Widely used by the general population, *B. pinnatum* species has several studies that dealt with the isolation and elucidation of its major compounds. Several classes of chemical compounds have been described for *B. pinnatum*, which includes fatty acids, acyclic and aromatic organic acids, amino acids, sugars, vitamins, minerals, bufadienolides, ketones, fenantrenics derivatives, sterols, flavonoids, long chain hydrocarbons, triterpenoids, phenolic acids, saponins and gums (Amaral et al., 2005). However, flavonoids, steroids and terpens are the compounds most frequently isolated from *B. pinnatum*. In relation to flavonoids, glycosylated derivatives from the quercetin, kaempferol and luteolin aglycones have been

Box 1: Chemical compounds reported for *Kalanchoe laciniata* species.

Plant part	Classification	Extract	Compound	Reference
Fresh leaves, green callus	Chlorophylls, carotenoids	Peroxide-free diethyl ether fraction of 80% (v/v) acetone–water extract	–	Stobart et al. (1967)
Fresh stems, leaves	Flavonoids	Juice	Kalambroside A (**1**); Kalambroside B (**2**); Kalambroside C (**3**); Patuletin 3-*O*-α-L-rhamnopyranosyl-7-*O*-(3‴-*O*-acetyl-α-L-rhamnopyranoside) (**4**); Patuletin 3-*O*-(4″-*O*-acetyl-α-L-rhamnopyranosyl)-7-*O*-(3‴-*O*-acetyl-α-L-rhamnopyranoside) (**5**); Patuletin 3-*O*-α-L-rhamnopyranoside (**6**); Patuletin 3-*O*-α-L-rhamnopyranosyl-7-*O*-α-L-rhamnopyranoside (**7**)	Costa et al. (1994)
Leaves	Flavonoids and carbohydrates	Aqueous and butanolic fraction of juice	–	Almeida et al. (1997)
Leaves	Flavonoids	Ethyl acetate extract	3,7-Di-*O*-α-L-rhamnopyranosyl-8-methoxy quercetin (**8**) 3,7-Di-*O*-α-rhamnopyranosyl-kaempferol (**9**) 3-*O*-α-L-rhamnopyranosyl-3,3′,4′,5,7-pentahidroxi-8-methoxyflavone (**10**)	Trevisan et al. (2006)
Leaves	Organic salt	Juice	Complexed between a hydro amino acid and malic acid (1:2)	Costa et al. (2006)
Dried leaves	Polysaccharides	–	–	Bhatti et al. (2013)
Fresh leaves	Flavonoids	Ethanolic extract 50%	Patuletin 3-*O*-α-L-rhamnopyranosyl-7-*O*-α-L-rhamnopyranoside (**7**)	Costa et al. (2015)



1 R_1=4"-*O*-acetyl-α-L-rhamopyranosyl; R_2=CH_3O; R_3=2"'-*O*-acetyl-α-L-rhamopyranoside; R_4=H; R_5=OH
2 R_1=α-L-rhamopyranosyl; R_2=OCH_3; R_3=2"'-*O*-acetyl-α-L-rhamopyranoside; R_4=H; R_5=OH
3 R_1=4"-*O*-acetyl-α-L-rhamopyranosyl; R_2=CH_3O; R_3=rhamopyranoside; R_4=H; R_5=OH
4 R_1=α-L-rhamopyranosyl; R_2=OCH_3; R_3=3"'-*O*-acetyl-α-L-rhamopyranoside; R_4=H; R_5=OH
5 R_1=4"-*O*-acetyl-α-L-rhamopyranosyl; R_2=CH_3O; R_3=3"'-*O*-acetyl-α-L-rhamopyranoside; R_4=H; R_5=OH
6 R_1=α-L-rhamopyranosyl; R_2=OCH_3; R_3=R_4=H; R_5=OH
7 R_1=α-L-rhamopyranosyl; R_2=OCH_3; R_3=α-L-rhamopyranosyl; R_4=H; R_5=OH
8 R_1=α-L-rhamopyranosyl; R_2=H; R_3=α-L-rhamopyranosyl; R_4=CH_3O; R_5=OH
9 R_1=α-L-rhamopyranosyl; R_2=H; R_3=α-L-rhamopyranosyl; R_4=CH_3O; R_5=H
10 R_1=α-L-rhamopyranosyl; R_2=H; R_3=H; R_4=CH_3O; R_5=OH

described for this species. Quercetin 3-*O*-α-L-arabinopyranosyl-(1 → 2)-*O*-α-L-rhamnopyranoside was the first derivative isolated for *B. pinnatum*, as reported by Muzitano et al. (2006a,b). Although quercetin is a common aglycone derivate, its 3-*O* diglycosidic bond is quite peculiar as it is a rhamnose–arabinose dimer that is not very common and in fact, has never been reported for leaves of other species of the genus *Kalanchoe* (Nascimento et al., 2015). This very peculiar molecule has been described for few species of other botanical families, but not as the major compound. Nascimento et al. (2018) state that this unusual flavonoid can be used as a marker for *B. pinnatum*. In addition, this major component has shown potent anti-inflammatory (Ferreira et al., 2014) and leishmanicidal (Muzitano et al., 2009) activities. The compounds already described for *B. pinnatum* are summarized in Box 2

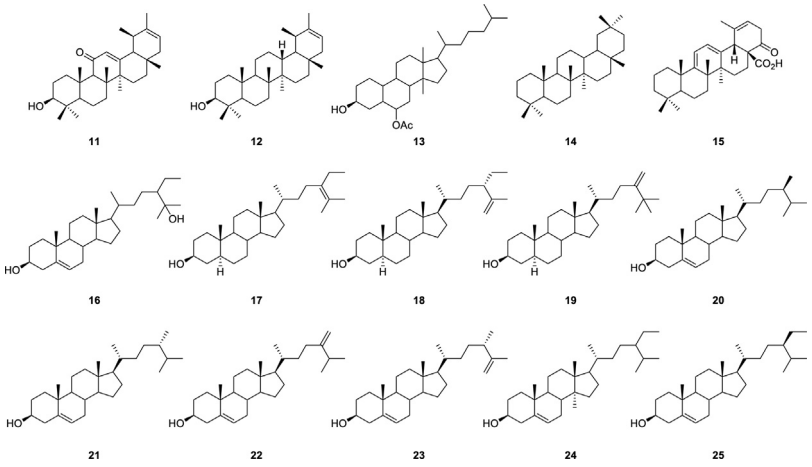
.

Box 2: Chemical compounds reported to *Bryophyllum pinnatum* species.

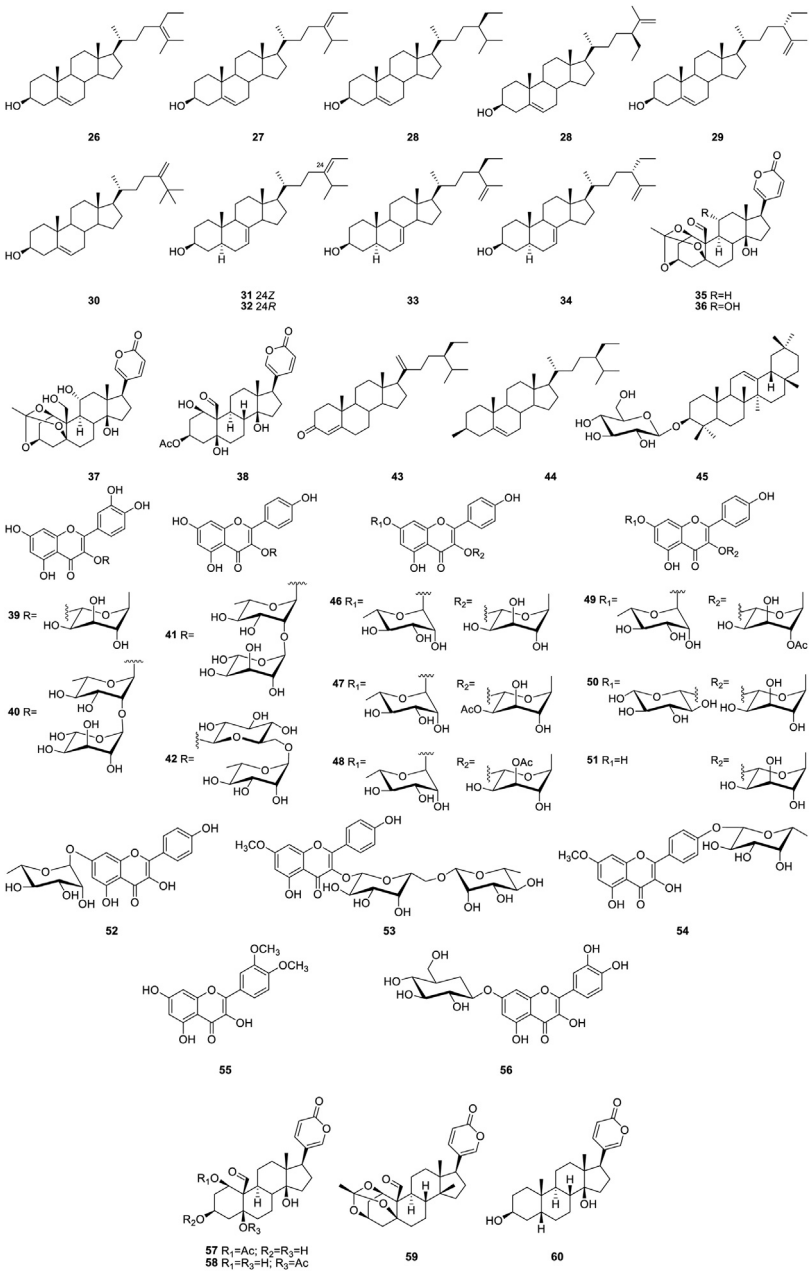
Plant part	Classification	Type of extract	Compound	Reference
–	Polysaccharides, minerals, flavonoids	Sap	Glycosylated derivatives of quercetin	Maksyutina and Zub (1969)
Leaves	Alkanes, triterpenes, steroids	Petroleum ether	C26–C34; α-amyrin; β-amyrin; Sitosterol	Gaind and Gupta (1972)
Fresh leaves	Organic acids, steroids, hydrocarbons, phenolic compounds, flavonoids	Methanolic extract	Bryophynol (**11**); Ψ-taraxasterol (**12**); Bryophyllol (**13**); 18α-oleanane (**14**); Bryophollone (**15**); bryophollenone; 24-ethyl-25-hydroxycholesterol (**16**)	Siddiqui et al. (1989)
Shoots	Steroids	Dichloromethane extract	Stigmast-24-enol (**17**); (24*S*)-stigmast-25-enol (**18**); 25-metylergost-24(28)-enol (**19**); (24*R*)-ergost-5-enol (**20**); (24*S*)-ergost-5-enol (**21**); ergost-5,24(28)-dienol (**22**); (24*S*)-ergosta-5,25-dienol (**23**); (24*R*)-stigmast-5-enol (**24**); (22*E*,24*S*)-stigmast-5,22-dienol (**25**); stigmast-5,24-dienol (**26**); (24*Z*)-stigmast-5,24(28)-dienol (**27**); (24*R*)-stigmast-5,25-dienol (**28**); (24*S*)-stigmast-5,25-dienol (**29**); 25-metylergost-5,24(28)-dieno (**30**); stigmast-7,24-dienol (**31**); (24*Z*)-stigmast-7,24(28)-dienol (**32**); (24*R*)-stigmast-7,25-dienol (**33**); (24*S*)-stigmast-7,25-dienol (**34**)	Akihisa et al. (1991)
Whole fresh plant	Bufadienolide orthoacetate	Chloroform fraction of the methanolic extract of the aqueous residue	Bersaldegenin-1,3,5-orthoacetate (**35**)	Xiuzhen et al. (1992)
Leaves	–	Acid fraction	89.3% of palmitic acid (C16), 10.7% of stearic acid (C18) and traces of arachidic (C20) and behenic acids (C22)	Almeida et al. (2000)
Leaves	Bufadienolides	Methanolic extract	Bryophyllin A (**36**)	Supratman et al. (2000, 2001)
Leaves	Bufadienolides	Methanolic extract	Bryophyllin C (**37**)	Supratman et al. (2001)
Leaves	Bufadienolides	Methanolic extract	Bersaldegenin-3-acetate (**38**)	Supratman et al. (2001)
Dried leaves	Alkaloids, flavonoids, phenols, tannins, vitamins, minerals	Aqueous, ethanolic, diethyl ether and 20% acetic acid extracts	–	Okwu and Jsiah (2006)
Fresh leaves	Flavonoid	Aqueous extract	Quercitrin (quercetin 3-*O*-α-L-rhamnopyranoside) (**39**)	Aoki et al. (2014), Cruz et al. (2008), Muzitano et al. (2006a,b)
Dried leaves	Minor vinylic aliphatic alcohol diglycoside	Ethanolic extract	1-Octen-3-*O*-α-L-arabinopyranosyl-(1 → 6)-β glucopyranoside	Almeida et al. (2006)
Leaves	Protein	Tampon TEGN	Rubisco (ribulose 1,5-bisphosphate carboxylase-/Oxigenase)	Abat et al. (2008)
Powdered plant	Alkaloids, tannins, steroids, flavonoids, sugars, organic acids	Petroleum ether, chloroform, methanolic, aqueous extracts	–	Devbhuti et al. (2008)
Leaves	Flavonoids	Aqueous extract	Quercetin 3-*O*-α-L-arabinopyranosyl (1 → 2) α-L-rhamnopyranoside (**40**); kaempferol 3-*O*-α-L-arabinopyranosyl (1 → 2) α-L-rhamnopyranoside (kapinnatoside) (**41**)	Cruz et al. (2008), Muzitano (2006)
Leaves	Phenolic acids, flavonoids	Ethyl acetate and methanol extract	Gallic acid; caffeic acid; coumaric acid; kaempferol-3-*O*-rutinoside (**42**)	Abdellaoui et al. (2010)
Dried leaves	Phenanthrene alkaloid	Ethanolic extract	1-Ethanamino-7-hex-1-yne-5′-one phenanthrene	Okwu and Nnamdi (2011a)
Powdered plant	Flavonoids	Ethanolic extract	5^{i} Methyl 4^{i},5,7-trihydroxyflavone 4^{i},3,5,7-Tetrahydroxy-5-methyl-5^{i}-propenamine; anthocyanidines	Okwu and Nnamdi (2011b)
Leaves	Bufadienolides, flavonoids, cinnamic acids	Juice	–	Wächter et al. (2011)
Roots	Steroids, alkaloids, saponins, glycosides flavonoids, tannins, carbohydrates, proteins, amino acids	Aqueous, chloroform, ethanol, ether extract	–	Majaz et al. (2011)
Leaves	Steroids, esters	Ethanolic extract	Stigmast-4,20(21),23-trien-3-one (**43**); stigmata-5-en-3β-ol (**44**); α-amyrin-β-D-glucopyranoside (**45**); *n*-undecanyl noctadec-9-en-1-oate; *n*-dodecanyl *n*-octadec-9-en-1-oate	Afzal et al. (2012)
Leaves	Alkaloids, glycosides, gums, saponins, tannins, reducing sugars	Chloroform extract	–	Biswas et al. (2012)

Box 2: Continued

Leaves	Phenols, flavonoids	Petroleum ether, chloroform, ethanol 95% extract	–	Bhatti et al. (2012)
Leaves	Cardiotonic glycosides, alkaloids	Chloroform extract	–	Mahata et al. (2012)
Leaves	Flavonoids	Methanolic extract	Kaempferitrin (**46**); kaempferol 3-*O*-α-L-(2-acetyl) rhamnopyranoside-7-*O*-α-L-rhamnopyranoside (**47**); kaempferol 3-*O*-α-L-(3 -acetyl) rhamnopyranoside-7-*O*-α-L-rhamnopyranoside (**48**); kaempferol 3-*O*-α-L-(4-acetyl) rhamnopyranoside-7-*O*-α-L-rhamnopyranoside (**49**); kaempferol 3-*O*-α-D-glucopyranoside-7-*O*-α-L-rhamnopyranoside (**50**); afzelin (**51**); α-rhamnoisorobin (**52**)	Tatsimo et al. (2012)
Air-dried powdered leaves	Flavonol glycosides	Petroleum ether extract	7-*O*-methylkaempferol-3-*O*-α-L-rhamnopyranosyl-(1 → 6)-*O*-β-D-galactopyranoside (**53**); kaempferol-14-*O*-α-L-rhamnopyranosyl-(1 → 3)-*O*-α-L-rhamnopyranosyl-(1 → 6)-*O*-β-D-galactopyranoside (**54**)	Bodakhe et al. (2013)
Dried leaves	Flavonol	Methanolic extract	3′,4′-Dimethoxy quercetin (**55**)	Darmawan et al. (2013)
Leaves	Flavonol glycosides, flavonoids, phenolic glycosides	Methanolic extract	4′-*O*-β-D-glucopyranosyl-*cis*-*p*-coumaric acid; syringic acid β-D-glucopyranosyl ester	Fürer et al. (2013)
Shoots	Steroid	Petroleum ether extract	Stigmasterol	Kamboj and Saluja (2017)
Leaves	Flavonoids, steroids, terpenoids, phenolics, alkaloids, glycosides, tannins.	Ethanolic extract	–	Joshi and Chauhan (2013)
Dried leaves	Flavonoid, phenolic acids	Ethyl acetate fraction of methanolic extract	Quercetin	Aoki et al. (2014) Chibli et al. (2014)
Dried leaves	Flavonoids, saponins	Aqueous extract	–	Alhaji et al. (2014)
Leaves	Flavonoids	Methanolic extract	Rutin; luteolin; luteolin 7-*O*-β-glucoside (**56**)	Chibli et al. (2014)
Leaves	Steroidal glycoside, bufadienolides	Methanol, ethylacetate, petroleum ether extracts	–	Tariq et al. (2015)
Leaves	Bufadienolides	Dichloromethane, ethanol extracts	Bersaldegenin-1-acetate (**57**); Bersaldegenin-3-acetate (**58**); Bersaldegenin-1,3,5-orthoacetate (**59**); Bufalin (**60**)	Oufir et al. (2015)
Leaves	Phenolic compounds	Acetone and methanol extracts	KPB-100; KPB-200	Cryer et al. (2017)



Box 2: Continued



Traditional uses

The traditional medicinal uses of *K. laciniata* and *B. pinnatum* are shown in Boxes 3 and 4 , respectively. As can be seen from these boxes, the leaf is the part of the plant mostly used by the population, whereas the juice is the most frequent mode of preparation for both species. Some of the properties are common for both species and those have been used to treat: (i) skin problems, (ii) problems in the respiratory system, (iii) pain, (iv) inflammation and (v) disorders in the gastrointestinal system. The inflammatory and gastric problems (ulcers and gastritis) are the most commonly treated disorders. In addition, *K. laciniata* and *B. pinnatum* have been used in the form of plaster or poultice to treat dermatological disorders and burn wounds. The antivenom activities of the leaves of both species against snake and scorpion bites have also been reported elsewhere.

The extract of *K. laciniata* leaves has been used for the treatment of chilblains, burns, erysipelas, wounds, cough, bronchitis, flu, gastritis, ulcers, otitis, kidney stone, diabetes, anxiety, microbial diseases, snakebite, pain and inflammation. In addition, it has been used to treat cancerous tumors, osteoarticular rheumatism, jaundice, yellow fever, other liver disorders, headache, prostate tumors and hemorrhoids. *K. laciniata* have been used mainly in the form of decoction, syrup, juice, poultice and maceration of its leaves (Silva et al., 2002). The popular uses of *K. laciniata* species are reported in Box 3.

The extract of *B. pinnatum* leaves have been used for the treatment of severe disorders such as gastritis, ulcers, cough,

Box 3: Medicinal popular uses of *Kalanchoe laciniata* reported in the literature.

Plant part	Popular use	Preparation	Reference
Leaves, stem	Otitis, skin diseases	–	Cos et al. (2002)
Leaves	Healing	–	Fonseca-Kruel and Peixoto (2004)
Leaves	Bronchitis, flu and sore	Juice, syrup and poultice	Medeiros et al. (2004)
Leaves	Ovarian and uterine inflammations	Pure juice or mixed with other plants for syrup preparation	Morais et al. (2005)
Leaves	–	Tea and syrup	Pereira et al. (2005)
Leaves	Ulcers and gastritis	–	Lisboa et al. (2006)
Leaves	Ulcers and gastritis	Juice	Silva et al. (2006)
Leaves	Coughing, gastritis, diabetes, pains in general	–	Albuquerque et al. (2007a)
Leaves	General pain, ulcer, gastritis, injury, general inflammation, asthma, lung problems, kidney stone	–	Albuquerque et al. (2007b)
Leaves	Chilblains, burns, wounds, erysipelas, ulcers, scurvy, flu and bronchitis	–	Boscolo and Valle (2008)
Leaves	Anxiolytic effects	–	Rodrigues et al. (2008)
Leaves	Respiratory system disorders	–	Leitão et al. (2009)
Leaves	Healing, flu and cough	Plaster, syrup and juice	Albertasse et al. (2010)
Leaves, root	Depurative, blood thinner, uterine inflammation, cough, influenza, expectorant, healing, pains in general, inflammation in general	Decoction, tincture, leave soaking, refreshment, licking, poultice, warm in oil or infusion	Cartaxo et al. (2010)
Aerial part	Fever, fracture, ear pain	Maceration	Hubert et al. (2013)
Leaves	To treat snakebite victims	Paste	Moura et al. (2015)
Leaves, aerial parts, roots, whole plant	Microbial diseases	Decoction, sap, maceration, heating in the ash	Ngezahayo et al. (2015)
Leaves	Facilitation of delivery, bleeding during pregnancy, postpartum abdominal pain	Decoction, maceration	Yemele et al. (2015)
Leaves	Snakebite	Paste	Moura et al. (2015), Félix-Silva et al. (2017)

bronchitis, various bacterial, viral and fungal infections, leishmaniasis, pain, inflammation, some tumors, respiratory infections, diabetes, hypertension, flu and fever (Perry and Metzger, 1980; Silva et al., 1995; Moreira et al., 2002; Medeiros et al., 2004; Amaral et al., 2005; Kamboj and Saluja, 2009). This species is part of the traditional Indian medicine. The part of the plant mostly used is its leaves, prepared as decoction, infusion, juice, syrup, poultice and paste. The popular uses of the species *B. pinnatum* are summarized in Box 4.

Pharmacological activities

The studies that investigated the pharmacological properties of *K. laciniata* and *B. pinnatum* usually assessed the activities of the juice or extracts from the leaves and/or aerial parts of these plants. Regarding the type of extract, most studies with *K. laciniata* used hydroethanolic, whereas for *B. pinnatum* the ethanolic (*in vitro*) and aqueous (*in vivo*) were the most commonly used extracts.

However, there is a large difference in the number of studies between the two species, being *B. pinnatum* the most studied one, therefore, following the trend that has already been observed in the chemical and ethnopharmacological studies, which had been previously discussed in this article. Fig. 4 presents an overview of the main pharmacological activities that have been studied (*in vitro* and *in vivo*) for the two species in addition to the number of studies that have been published so far for each plant.

It is clear from Fig. 4 that a larger number of studies have been reported for *B. pinnatum*, which suggests that there is more room for studies that investigate additional pharmacological activities for *K. laciniata*, especially *in vivo* studies. Moreover, this figure indicates that the gastroprotective activity (alti-ulcer, for instance) is not well explored yet for these plants, especially for *K. laciniata*.

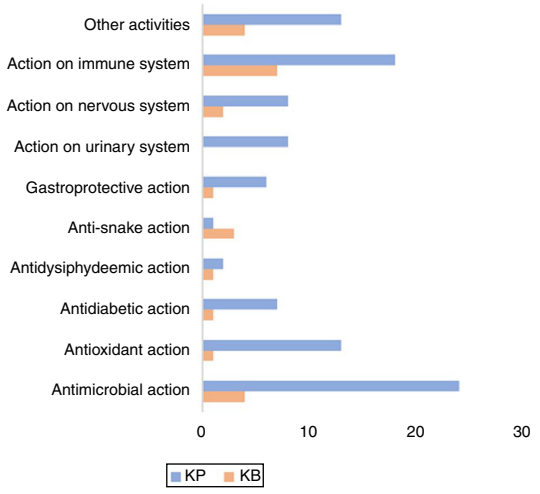


Fig. 4. Graphical representation of the number of pharmacological studies for *Kalanchoe laciniata* and *Bryophyllum pinnatum*.

It is worth to point out that no comparative study between these species has been carried out so far, especially those related to pharmacological aspects. There are only two studies, Fernandes et al. (2016) and Araújo et al. (2018), which compare the anti-snake and gastroprotective activities, respectively. Thus, more studies that compare some pharmacological activities between *K. laciniata* and *B. pinnatum* would be interesting to see, especially those related to their traditional uses.

Kalanchoe laciniata

Several non-clinical assays related to the evaluation of pharmacological activities of *K. laciniata* are described in the literature.

Box 4: Medicinal popular uses of *Bryophyllum pinnatum* described in the literature.

Plant part	Popular use	Preparation	Reference
Leaves	Bruises, swellings	Raw leaf applied directly to the affected area	Arnason et al. (1980)
Not reported	Tonic	–	Mello (1980)
Leaves	Otitis, sinusitis	–	Sandberg and Cronlund (1982)
Leaves	Boils, sores	Warm leaf juice applied over the injured area two or three times a week. Leaves are bound on wounds to hasten suppuration	Sebastian and Bhandari (1984)
Not reported	Dermatological disorders	–	Esquivel and Zolla (1986)
Leaves	Leprous sores and motor disorders. Fever	The leaves are dry-fried and used in a complex preparation. The juice of the leaves is rubbed on the forehead to reduce fever	Elliott and Brimacombe (1987)
Not reported	Cancer	–	Mathew and Unithan (1992)
Leaves	Scabies, leucoderma	Juice and decoction	Bhandary et al. (1995)
Leaves	Hypertension	Decoction	Longuefosse and Nossin (1996)
Leaves	Constipation, fever	Juice	Ong and Nordiana (1999)
Not reported	Inflammation, stomach pain	Tea	Muñoz et al. (2000)
Leaves	General pain, cough, bronchitis, flu, pneumonia, dermatitis	–	Begoss et al. (2002)
Leaves	Bronchitis, ulcers, chilblain treatment, at syrup form	Juice with milk and smear leaves	Moreira et al. (2002)
Whole plant, leaf	Rheumatoid arthritis, tummy bug, injuries from falls, numbness of limbs, bruise, burn, ulcer	Medicine bath, rubbing or massage	Long and Li (2004)
Leaves	Cough, bronchitis, chilblain, ulcer	Syrup, juice with milk, smear leaves	Medeiros et al. (2004)
Leaves	Bladder problems, "cooling", kidney and other urinary problems, bladder stones, hypertension, high cholesterol	–	Lans (2006)
Leaves	Abscess	The leaves are crushed and the paste is layered on the boils	Saikia et al. (2006)
Leaves	Analgesic, psychotropic	Decoction, squeezed sap after healing, boiled	Banzouzi et al. (2008)
Leaves	Relieve abdominal and back pain, stop postpartum abdominal pain, stop excessive menstrual hemorrhage, reduce fever	Decoction, poultice	Coe (2008)
Leaves	Burn, wound	Pounded Liniment and poultices	Inta et al. (2008)
Leaves	Wounds, bruises, boils, jaundice, snakebite, dysentery, urinary trouble and quick healing of wounds	–	Sikdar and Dutta (2008)
Leaves	Gastritis, ulcer, kidney, dry cough with chest pain, cough, erysipelas, any swelling, cataract, ulcer	Mixture, syrup, cataplasm, mixture or compress, distillate, "*garrafada*"	Coelho-Ferreira (2009)
Leaves	Fever, headache, nausea, wound	Direct application of the leaves on the site	Giovannini and Heinrich (2009)
Leaves	Coughs, mucus, fever, sudden loss of consciousness (epilepsy-like), constipation, piles	Juice squeezed from the leaves is taken two teaspoonfuls twice daily. Paste of leaves is applied to rectum	Hossan et al. (2009)
Leaves	Kidney stone	One teaspoonful juice was taken twice a day up to 1 month	Kosalge and Fursule (2009)
Leaves	Asthma	Heated on low fire, sap squeezed, mixed with melasse (juice of *Saccharum officinale* and juice of *Citrus aurantifolia* and drunk	Ruysschaert et al. (2009)
Leaves	Headache, pain, depurative if high dose – emetic; *mal aire*	Crushed and rubbed on the forehead; squeezed, the juice obtained is drunk; slightly boiled, for drinking and bathing (for children)	Sanz-Biset et al. (2009)
Leaves	Lumbar pain	In natura – plaster	Garcia et al. (2010)
Leaves	Cancer, inflammation	Infusion	Kamboj and Saluja (2009)
Leaves	Migraine, headache	Juice with coconut or andiroba oil	Kamboj and Saluja (2009)
Leaves	Furuncle, skin ulcers	Heat the leaves and use them topically	Kamboj and Saluja (2009)
Seed	Stye disease	Juice obtained from crushed seeds is applied to eyes (1–2 drops, 2–3 times daily)	Rahmatullah et al. (2010)
Leaves	Headache	Crumpled leaf application	Boulogne et al. (2011)
Leaves	Liver problems	*In nature*	Costa and Mayworm (2011)
Leaves	Bone pain, inflammation, muscular-skeletal system disorders (broken bone)	Crushed and compressed	Panyaphu et al. (2011)
Leaves	Bone fracture, constipation and kidney stone problem	Paste (topical) and water decoction with sugar (oral)	Tangjang et al. (2011)
Leaves	Antidiabetic	Juice of boiled leaves (100 g) is prescribed orally twice a day	Tarak et al. (2011)
Leaves	Cuts	–	Bhat et al. (2012)
Leaves	Stomach ulcer	Raw leaves eaten daily in empty stomach	Bosco and Arumugam (2012)
Leaves, roots	Hypertension	Decoction, infusion, mixture	Gbolade (2012)
Leaves	Wart. Skin diseases, wounds, scabies, stop bleeding	Prepare a poultice and apply on wart	Nunkoo and Mahomoodally (2012)

Box 4: Continued

Leaves	Scorpion sting Venomous insect bite, rheumatism, stiff joints, kidney stones	Paste (external)	Prabu and Kumuthakalavalli (2012), Bahekar et al. (2012)
Leaves	Treating amenorrhea Treating morning sickness	Hot infusion	Srithi et al. (2012)
Leaves	Sexual transmitted infections (gonorrhea)	A mixture of chopped leaves, chopped Opuntia stricta stem and Euphorbia hypericifolia (whole plant) all boiled in 2 l of water and administered once a day as an enema	Wet et al. (2012)
–	Gastrointestinal disorders	The dose is 45–180 grains mixed with twice its amount of melted butter	Kadir et al. (2013)
Leaves	Remove kidney stone, bladder, pancreatic, emollient	Extract, paste	Mahmood et al. (2013)
Aerial herbal material	Guinea worm	Poultice as a paste and decoction	Agyare et al. (2014)
Leaves	Eczema, pruritus	–	Bhat et al. (2014)
Leaves, flower	Diabetes, hypertension, analgesic, inflammation, wound ulcers, anti-parasitic, insect bites, anti-cancer, cough, diarrhea, sedative, diuretic, anti- microbial, convulsions	Juice extract	Ezuruike and Prieto (2014)
Leaves, root	Cholera, diarrhea, and dysentery, ulcer, urinary diseases, gastrointestinal disorders	Juice, decoction Leaf juice and decoction of root	Islam et al. (2014)
Leaves	Kidney stone	1 cup (50 ml) fresh juice three times a day for 5–10 days or till removal of stones	Choudhury et al. (2014)
Leaves	Coughing, whooping cough	2–3 spoonful of leaf paste is taken as drink 2–3 times daily for 3 weeks	Kadir et al. (2014)
Leaves	Pain in the feet, diabetic neuropathy (diabetes and related complications)	Prepare a decoction with the leaves and use it as a footbath	Mootoosamy and Mahomoodally (2014)
Leaves	Snakebite	1–2 spoons of leaf decoction are given every 1 h after snakebite	Félix-Silva et al. (2017), Sarkhel (2014), Sikdar and Dutta (2008)
Leaves	Legs pain, body ache, antimicrobial, anti-ulcer, antinociceptive, anti-inflammatory, antidiabetic, neurosedative and muscle relaxant, hepatoprotective, joint pain (rheumatism)	Decoction Heated oil is applied evenly on leaf which is carefully tied to pain site. Bath with decoction of leaves for legs pain and body ache	Sreekeesoon and Mahomoodally (2014)
Leaves	Stone disease, kidney stone	–	Agarwal and Varma (2015)
Leaves	Allergy, dysentery	Crushed extract	Choudhury et al. (2015a)
Leaves	Digestive system disorder	Extract from the crushed leaves	Choudhury et al. (2015b)
Leaves	Malaria, fever	Leaves juice (orally administered) for malaria and fever	Frausin et al. (2015)
Leaves	Cold	Decoction, juice	Picking et al. (2015)
Whole plant	Diabetes	Fresh juice	Tarafdar et al. (2015)
Leaves	Menstrual pain, kidney stone, worms in stomach	–	Xavier et al. (2015)
Stem, leaves	Antitumor activity	–	Tene et al. (2007) *apud* Bailon-Moscoso et al. (2015)
Leaves	Sprain	Leaves decocted or grilled on fire. Applied the leaves on the affected limb for few hours	Chassagne et al. (2016)

Several non-clinical studies have investigated the numerous pharmacological activities of *K. laciniata*. Summaries of the non-clinical *in vitro* and *in vivo* studies are presented in Boxes 5 and 6 , respectively.

Regarding the non-clinical *in vivo* studies, anti-inflammatory and immunomodulatory have been the most frequently investigated activities so far. This fact is probably due to the popular use of *K. laciniata* for treating inflammatory disorders. Besides these activities, *K. laciniata* have been investigated to treat against snake bites by *Bothrops* species, *B. jararaca* and *B. arternus*, where it showed great potential to ameliorate the local effects induced by the snake venom, especially the hemorrhagic reaction. Finally, although often recommended by folk medicine practitioners to use *K. laciniata* for gastroprotection, there is only one article that investigated its potential use to treat gastric ulcer. Therefore, there are so many pharmacological activities that still lack investigation on this species.

Bryophyllum pinnatum

Several non-clinical *in vitro* and *in vivo* studies have been reported for *B. pinnatum* as summarized in Boxes 7 and 8 , respectively. In contrast to the *K. laciniata* species where most studies investigated its anti-inflammatory activity, the studies performed for *B. pinnatum* evaluated its leishmanicidal, anti-diabetic, anti-inflammatory, immunomodulatory and anti-cancer properties.

B. pinnatum is used in folk medicine to treat various diseases. For this reason, several *in vitro* studies were carried out in order to verify the pharmacological properties of those species, which includes hepatoprotective, leishmanicide, immunomodulatory, antimicrobial, antioxidant, anticancer, and antiurolithiatic activities. Studies have shown the potential activity of *B. pinnatum* against hematological parasites such as *Leishmania*, *Plasmodium* and *Trypanossoma*, whose properties are important due to the very limited pharmacological alternatives for treating these neglected diseases, where researches in this area are of outmost importance.

Box 5: Non-clinical *in vitro* studies performed for *Kalanchoe laciniata*.

Plant part	Extract/fraction/compound	Method	Result	Reference
Reversible and time-dependent inhibitory effects on CYP2C19 and CYP3A4 activities				
Whole herb	Methanol extract	Crude methanol extract and fractions of *K. crenata* were incubated and preincubated with recombinant human CYP2C19 and CYP3A4.	A significant time-dependent inhibition of tested samples on CYP3A4 with crude methanol and fractions were observed.	Awortwe et al. (2015)
Leishmanicidal activity				
Aerial parts	Mixture of solvents consisting of methanol and methylene chloride (v/v)	Antileishmanial activity against promastigotes forms of *L. donavani* – cell viability.	The *K. crenata* showed no activity against promastigotes forms of *L. donavani*.	Hubert et al. (2013)
Antibacterial activity				
Aerial parts (leaves and stems), essential oil	Hydroalcoholic extract (leaves), the alcohol (stems), essential oil (leaves)	Diffusion in solid medium method to determination of the minimum inhibitory concentration (MIC).	Only the essential oil showed activity against methicilin resistant *Staphylococcus aureus* (MRSA). This action was considered bacteriostatic with the reduction to one $\log_{10}$ CFU/ml after 6 h of exhibition at the concentrations 4 and 8%.	Silva et al. (2009)
Antiviral activity				
Leaves	Aqueous extract	Antiviral activity against herpes virus bovine HBV type I.	The extract showed reasonable antiviral activity, with inhibition index $10^{-4.48}$ and high therapeutic index (88.16%).	Schiavo (2005)
Acetylcholinesterase inhibition				
Leaves	Hexane, methanol, ethyl acetate extract	Microplate assay with the enzyme acetylcholinesterase (AchE).	The methanol and ethyl acetate showed 100% inhibition at the concentration 2 mg/ml. The ethyl acetate had IC_{50} 0.16 mg.	Trevisan et al. (2006)
Leaves	Ethyl acetate, methanol extracts	Microplate assay based on Ellman's method and TLC (thin-layer chromatography) assay.	In the microplate assay, the ethyl acetate and methanol extracts showed 100% inhibition. The ethyl acetate extract presented IC_{50} 0.16 mg/ml. In the TLC assay, the ethyl acetate extract showed positive/false-positive result and methanol extract showed negative result.	Feitosa et al. (2011)
Thyroid peroxidase inhibition				
Leaves	Aqueous extract	TPO (thyroid peroxidase) of tissue samples obtained during thyroidectomy.	At the dose 2 μM, the extract caused significant inhibition of TPO iodine-oxidation activity.	Ferreira et al. (2000)
Larvicide activity				
Leaves	Hexane, methanol, ethyl acetate extract	Larvicide activity against *Aedes aegypti* gnat larvae.	Significant larvicide activity to hexane and ethyl acetate extracts, but not to isolated flavonoid (3-*O*-α-LL-rhamnopiranosil-3,3′,4′,5,7-pentahydroxi-8-metoxiflavon) at the concentration of 500 ppm.	Trevisan et al. (2006)
Antihistaminic activity				
Leaves	Juice (without solvents), aqueous, butanol fractions	Assays with Guinea pig ileum.	The juice and fractions changed response curve to histamine, displaying an antihistamine effect.	Almeida et al. (1997)
Lymphoproliferative activity				
Leaves	Juice (without solvents) and isolated compounds (Box 1 compound **1–7**)	Lymphoproliferative activity in human lymphocites.	The concentration of flavonoids 2 (0.25 μg/ml) and 1 (0.5 μg/ml) that inhibited the lymphocyte proliferation was 80 and 40 times, respectively, greater than the juice (20 μg/ml).	Costa et al. (1994)
Anti-inflammatory activity				
Leaves	Juice (without solvents)	Inflammation induced by Zymozan.	The inhibition of lymphocytes proliferation was dose-dependent, with the inhibitory concentration of 50% at 50 μg/ml.	Ibrahim et al. (2002)
Antioxidant activity				
Whole plant	Methanol extract	TBARS (thiobarbituric acid-reactive substances), MDA (malondialdehyde) activity, SOD (superoxide dismutase) activity and CAT (catalase) activity.	Treatment of the rats with the extract for six weeks lowered MDA level by 34–44%, but increased CAT levels by 78–176%, and SOD levels by 116–257%.	Fondjo et al. (2012)
Phospholipase A_2 activity				
Leaves	Hydroethanolic extract	Phospholipase A_2 activity was determined turbidimetrically in 96-well microplates using an egg yolk suspension.	The extract showed significant inhibitory activity of PLA_2.	Fernandes et al. (2016)

Box 6: Non-clinical *in vivo* studies performed for *Kalanchoe laciniata*.

Plant part	Extract/fraction/ compound	Dose and rout	Method	Animal model	Result	Reference
Anti-inflammatory activity						
Leaves	Aqueous 1 (before flowering) Aqueous 2 (after flowering)	0.25, 0.5, 1.0, 2.0 g/kg, *i.p.*	Paw edema induced by carrageenan	Wistar rats	All concentrations of extract 1 inhibited the paw edema 4 h after carrageenan injection, while the extract 2 showed no anti-inflammatory activity.	Mourão et al. (1999)
Aerial parts	Juice and a product of juice purification (KMC)	480 mg/kg (juice), *i.p.*; 240 mg/kg (kalanchosine dimalate – KMC – in water), *i.p.*	Paw edema induced by zymosan	C57B110 male mice	The dose 240 mg/kg, *i.p.*, KMC significantly reduced the rats popliteal lymphonodes increasing. The dose 480 mg/kg, *i.p.*, of juice of *K. laciniata* obtained the similar result, indicating that KMC is at least twice more active then the juice.	Costa et al. (2006)
Leaves	Methanol extract	300, 600 mg/kg, oral	Paw edema induced by carrageenan	Wistar rats	The dose 600 mg/kg exhibited the maximum anti-inflammatory effect (43.47%) in 30 min.	Dimo et al. (2006)
Adjuvant treatment to poisoning (local anti-inflammatory activity)						
Aerial parts	Aqueous extract	Extract and topic formulation (3:7 – extract:lanette cream)	Hemorrhagic activity induced and by *Bhotrops alternus*	Adult mices	The extract and the formulation showed significant results in reducing edema, hemorrhagic halo and necrosis prevention induced by *Bothrops alternatus* venom.	Fonseca et al. (2004)
Leaves	Aqueous extract	Preincubation of venom with the extract	Hemorrhagic assay induced by *B. jararaca*	Swiss mice	In the concentration 1:48 the extract showed a significant reduction in hemorrhage (57%).	Moura et al. (2015)
Leaves	Hydroethanolic extract	125, 250, 500 mg/kg, *i.p.*	Paw edema and hemorrhagic activity induced by *Bhotrops jararaca*	Swiss albino mice	In pre-treatment protocol, the extract reduced the hemorrhagic activity reaching about 40%, and in the post-treatment protocol, it did not show activity. In the antiendematogenic activity, *K. laciniata* did not show any antiendematogenic activity in both treatment protocols.	Fernandes et al. (2016)
Immunomodulatory activity						
Leaves	Aqueous extract	200 µl, oral; 160, 320, 480 or 960 mg/kg, *i.p.*	Paw edema induced by zymosan	C57B110 male mice	The inflammation was reduced after 7 days of treatment.	Ibrahim et al. (2002)
Aerial parts	Product of juice purification (w/o use of solvents): KMC	480 mg/kg of juice and 160 mg/kg of KMC (kalanchosine dimalate), *i.p.*	Administration of juice and KMC at the mice with posterior removal of cells for analysis	C57BL/10 and C57BL/10ScCr male mice	KMC promoted selective inhibition of B-cell lymphopoiesis, by inhibiting IL-7.	Paiva et al. (2008)
Anti-dyslipidemic potential						
Whole plant	Methanolic extract	50, 68 mg/kg, oral	Diabetes and nephropathy were induced in the rats with streptozotocin	Male Wistar rats	After six weeks of treatment, the doses reduced the blood level of the glucose, the triacylglycerides, the total cholesterol and the LDL cholesterol. The HDL level was enhanced and hence decreased the atherogenic index. The extract reduced the glucosuria and proteinuria.	Fondjo et al. (2012)
Antihyperglycaemic potential						
Whole plant	Hydroethanolic extract	135, 200 mg/kg, oral	Diabetes was induced by hypercaloric sucrose diet over 4 months	Adult male Wistar rats	Both doses reduced the blood glucose levels in normal and diabetic rats without real dose-dependant effect, 6 h after a single oral administration.	Kamgang et al. (2008)
Analgesic activity						
Leaves	Methylene chloride/methanol (1:1) extract	150, 300 mg/kg, oral	Writhing test, Formalin test and Analgesy meter test	Adult Swiss albino mice and adult Wistar rats	The extract significantly reduced the writhing reaction induced by acetic acid, reduced the licking time at the first phase of observation, in the second phase, animals treated showed no sign of pain and reduced the animal's sensitivity to pain.	Nguelefack et al. (2006)

Box 6: Continued

Plant part	Extract/fraction/compound	Dose and rout	Method	Animal model	Result	Reference
Anticonvulsant activity						
Leaves	Methylene chloride/methanol (1:1) extract	150, 300, 600 mg/kg, oral	Pentylenetetrazol, Thiosemicarbazide and Strychnine sulphate-induced seizures	Adult Swiss albino mice and adult Wistar rats	The extracts increased the latency period and reduced the duration of seizures in a dose dependent manner. The dose 600 mg/kg delayed the onset of convulsion and reduced the duration of convulsion.	Nguelefack et al. (2006)
Cardiovascular effects						
Leaves	*n*-Butanol extract	2, 5, 10 mg/kg, *via* cannula in the right femoral vein	Effect of extract on blood pressure, heart rate, ECG	Guinea pigs	The slow administration of the *n*-butanol extract resulted in a significant transient fall in blood pressure that lasted for 4 min, induced a dose dependent fall in heart rate and a modification of the electrocardiogram curve.	Nguelefack et al. (2008)
Antitumor activity						
Leaves	Hydroethanolic extract	62.5, 250 mg/kg, *i.p.*	Implant in mice tumor cells: Ehrlich carcinoma and sarcoma-180	Female albino Swiss mice	Both doses showed an upper inhibition to 50% for sarcoma-180. For Ehrlich Carcinoma, the highest inhibition was 66.59% for the higher dose.	Silva (2007)
Leaves	Aqueous extract	50 mg/kg, *i.p.*	Antitumor activity in mice infected with sarcoma-180	Female albino Swiss mice	The extract showed inhibitory effect of tumor growing against sarcoma-180, with tumor mass reduction 52.8%.	Machado and Melo-Júnior (2009)
Gastroprotective						
Leaves	Aqueous extract	125, 250, 500 mg/kg, oral	Gastrics lesions induced by ethanol and indomethacin	Female Wistar rats	The pre-treatment protects the mucosa of rats against the gastric damage and significantly reduced damage by improving parameters related to oxidative stress and inflammation on mucosal structures.	Araújo et al. (2018)

The potential use of *B. pinnatum* against *Leishmania amazonensis* has been investigated *in vitro* (Muzitano et al., 2006a,b) and *in vivo* (Muzitano et al., 2009), where the authors demonstrated such activity with the leaves extract (320 mg/kg body weight), as well as with the isolated flavonoids, 3-*O*-α-L-arabinopyranosyl (1 → 2)-α-L-rhamnopyranoside and quercetrin (16 mg/kg body weight), with both being able to significantly reduce parasite load (Muzitano et al., 2009). In the same article, Muzitano et al. (2009) studied the oral metabolism of flavonoids from *B. pinnatum* in a murine model of cutaneous leishmaniasis. In addition, they performed another study investigating the influence of cultivation conditions, season of collection and extraction method on the content of antileishmanial flavonoids, where they demonstrated that active flavonoids were more abundant when the leaves were collected during the summer season and after aqueous extraction at 50 °C.

Regarding the *in vivo* studies, the most investigated activities are leishmanicidal, hepatoprotective, immunoprotective, anti-inflammatory, anti-ulcer, antihypertensive, antinociceptive, wound healing, anti-asthmatic, antitussive, antidiabetic and anticonvulsant. Although these studies have demonstrated the several pharmacological activities attributed to *B. pinnatum*, it seems that its full potential is far from being proved and additional studies are needed in order to fully investigate its pharmacological properties, its mechanisms of action and its pharmacokinetics.

Another interesting area of research is the anti snake-bite activity. Snake-related accidents are a serious public health problem and have been included on the WHO's List of Neglected Tropical Diseases since 2009 (Gutiérrez et al., 2013). Fernandes et al. (2016) investigated the activity of *B. pinnatum* against the local effects induced the venom of *B. jararaca*, where they showed that the extract of this plant was able to antagonize the hemorrhage and edema as well as to inhibit the phospholipase A2 from the venom. The extract of *B. pinnatum* was active in pre- and post-treatment protocols, indicating the potential antiophidic activity of *Kalanchoe* species against local effects induced by *B. jararaca* snake, suggesting their potential use as a new source of bioactive molecules against bothropic venom.

Unlike *K. laciniata*, the antiulcer activity of *B. pinnatum* has been studied extensively in recent years. The work published by Araújo et al. (2018) showed that the pre-treatment with *B. pinnatum* juice protects the mucosa of rats against the gastric damage of indomethacin and ethanol-induced gastric lesions and reduced damage by improving parameters related to oxidative stress and inflammation on mucosal structures. However, additional studies are necessary in order to investigate what active components are responsible for such activity and the mechanisms of action involved. In addition, further clinical studies are necessary to prove the gastroprotective activity of *B. pinnatum* in humans.

In this current literature review, only one clinical study was found that evaluated the efficacy and safety of capsules containing *B. pinnatum* extract in the treatment of overactive bladder syndrome. The clinical study of phase II, prospective, multicenter, double-blind randomized, placebo-controlled was conducted with twenty female patients and suggests that this species might have potential use in the treatment of overactive bladder (Betschart et al., 2013). In addiction to this article, the same research group investigated the effects of the leaves juice, fractions enriched in flavonoids and bufadienolides as well as a flavonoid aglycone mixture and individual aglycones on detrusor contractility as a major target in overactive bladder treatment, where the authors found that several

Box 7: Non-clinical *in vitro* studies performed for *Bryophyllum pinnatum*.

Plant part	Extract/fraction/compound	Method	Result	Reference
Anti-helmintic activity				
Aerial herbal material	Hydroethanolic (50:50, v/v) extract	Anti-helmintic activity against the free-living model nematode *Caenorhabditis elegans*	No activity was observed for the extract of *B. pinnatum*.	Agyare et al. (2014)
Antibacterial and antifungal activities				
Leaves	Methanolic extract (60%)	Agar-well diffusion method	Five of the tested bacteria (*Bacillus subtilis*, *Escherichia coli*, *Proteus vulgaris*, *Shigella dysenteriae* and *S. aureus*) were sensitive to extract at 25 mg/ml. *K. pneumoniae*, *P. aeruginosa* and *C. albicans* were resistant to the extract.	Akinpelu (2000)
Leaves	Ethanolic extract (70%)	Agar-well diffusion method	Broad-spectrum antimicrobial activity was detected in crude extracts, being active against Gram-positive and Gram-negative bacteria, yeast and filamentous fungi (*C. albicans*, *Rhizoctonia bataticola*, *A. niger* and *Alternaria alternate*).	Aqil and Ahmad (2003)
Leaves	Aqueous, methanolic extracts, extract with Palmwine and with gin and with brew corn	Agar-well diffusion, MIC and minimum bactericidal concentration (MBC)	The methanolic extract was most active, inhibiting *S. aureus, Enterococcus faecalis*, *B. subtilis* e *P. aeruginosa*. The other extracts showed moderate activity.	Akinsulire et al. (2007)
Leaves	Alcoholic (90%), aqueous extract	Cup Plate Method (Zone of Inhibition)	The most active extract was the aqueous one followed by the alcoholic extract. The susceptibility decreasing order for the aqueous extract: *Enterobacter aerogenes* > *E. coli* > *Shigella dysenteriae* > *Salmonella enterica* var. Typhi > *S. aureus* > *B. subtilis* > *Staphylococcus epidermidis* > *Micrococcus luteus*. And for the ethanolic extract: *S. aureus* > *S. enterica* var. Typhi > *S. dysenteriae* > *E. aerogenes* > *E. coli* > *B. subtilis*.	Jain et al. (2010)
Stem	Methanolic, aqueous extracts	Agar-diffusion method	The methanol extract had significant antibacterial action against *B. subtilis* and *S. aureus* at 100, 50 and 25 mg/ml. Also, the aqueous extract presented antibacterial effect against *S. enterica* var. Typhi and *B. subtilis* at the same concentrations.	Nwadinigwe (2011)
Leaves, stems	Petroleum ether, aqueous extracts	Agar-disc diffusion method	Both extracts showed moderate activity against all tested fungal strains (*A. niger*, *Blastomyces dermatitides*, *C. albicans*, *Pityrosporum ovale*, *Trichophyton* spp. and *Microsporum* spp.). The petroleum ether extract was more effective against *Microsporum* spp., whereas *C. albicans* was more susceptible to aqueous extract.	Chowdhury et al. (2011)
Leaves	Chloroform extract	Agar-disc diffusion method	The extract exhibited low level of antibacterial activity against *B. subtilis*, *B. megaterium*, *S. aureus*, *E. coli*, *P. aureginosa*, *S. enterica* var. Typhi and *S. dysenteriae*. The highest inhibition was against *E. coli*, while no antibacterial activity was found against *V. cholerae*.	Biswas et al. (2012)
Whole plant	Methanolic extract	Disk-diffusion method	The methanol exhibited weak antimicrobial effect against *B. cereus*, *Bacillus megaterium*, *B. subtilis*, *Sarcina lutea*, *S. aureus*, *E. coli*, *Salmonella entérica* var. Typhi, *Salmonella paratyphi*, *Shigella boydii*, *S. dysenteriae*, *P. aeruginosa*, *Vibrio mimicus*, *Vibrio parahaemolyticus*, *Aspergillus niger*, *C. albicans* and *Sacharomyces cerevisiae*.	Sharker et al. (2012)
Whole plant	Methanolic extract	MIC	The extract presented antibacterial and antifungal activities with MIC values ranging from 32 to 512 μg/ml. The microorganisms tested were *S. aureus*, *P. aeruginosa, Salmonella enterica* var. Typhi, *C. albicans*, *Candida parapsilosis* and *Cryptococcus neoformans*.	Tatsimo et al. (2012)
Root, stem, leaf and whole plant	Methanolic, aqueous extracts	MIC, agar-well diffusion method	The stem methanolic extract showed higher antibacterial activity being effective against *Corynebacterium diphtheriae*, *Micrococcus luteus*, *B. subtilis*, *Alcaligenes faecalis*, *Bordetella bronchiseptica* and *Serratia marcescens*. Aqueous extract of leaf was only active against *B. subtilis* and *A. faecalis*, while methanolic extract had no activity.	Sharma et al. (2014)
Leaves	Methanolic and ethyl acetate extracts	Anti-*Helicobacter* activity for determination of MIC and MBC	Methanol extract showed a significant anti-*Helicobacter* activity with MIC and MBC values of 32 and 256 μg/ml, respectively	Mabeku et al. (2017)
Antitrypanosomal activity				
Leaves	Aqueous extract	Micro titer plate method	No observable reduction in motility at 10 mg/ml, motility reduced slightly at 20 mg/ml and highly reduced motility at 40 mg/ml.	Alhaji et al. (2014)

Box 7: Continued

Plant part	Extract/fraction/compound	Method	Result	Reference
Anti-hepatitis C virus activity				
Leaves	Methanolic extract	HUH7it-1 cells (human hepatocellular carcinoma) were infected with the HCV genotype 2a strain JFH1 in the presence of crude methanol extracts	The crude methanol extract exhibited anti-HCV activity with a IC_{50} 17.2 μg/ml.	Aoki et al. (2014)
Antiplasmodial activity				
Leaves	Ethanolic extract	SYBR green I-based fluorescence assay	Good antiplasmodial activity (IC_{50} 11–20 μg/ml) was observed in leaf ethanol extract.	Singh et al. (2015)
Leishmanicide activity				
Leaves	Aqueous extract, isolated flavonoid	Antileishmania activity against *Leishmania amazonensis* (antiamastigote and antipromastigote)	The aqueous extract and the flavonoid isolated showed activity against *Leishmania amazonensis.*	Muzitano et al. (2006a)
Antioxidant activity				
Leaves	Aqueous extract	DPPH and oxide radical scavenging, reducing power, antilipidic peroxidation	The extract had significant antioxidant and oxidative radical scavenging activities.	Harlalka et al. (2007)
Leaves	Methanolic extract	DPPH radical scavenging	A dose dependent radical scavenging activity was observed with the maximum activity (63.97%) at the highest dose comparable to the standard BHT.	Gupta et al. (2009)
Leaves	Alcoholic, aqueous extract	DPPH scavenging method	The aqueous extract presented more antioxidant activity then the alcoholic one. Aqueous and alcoholic extracts and ascorbic acid exhibited 74.7, 58.4 and 88.6% inhibition, respectively, and the EC_{50} (μg/ml) –144.23, 117.42 and 96.15 μg/ml, respectively.	Jain et al. (2010)
Roots	Aqueous, ether, chloroformic, methanolic extracts	DPPH and oxide radical scavenging methods, reducing power	The methanolic extract had more effective antioxidant activity then the other extracts.	Majaz et al. (2011)
Whole plant	Methanolic extract	Method of Brand-Williams	A significant antioxidant activity was verified.	Sharker et al. (2012)
Whole plant	Methanolic extract	DPPH radical scavenging method	The methanolic extract showed antioxidant activity with an IC_{50} of 52.48 μg/ml.	Tatsimo et al. (2012)
Leaves	Aqueous extracts	DPPH radical scavenging method	Supplemental blue light improved the antioxidant activity.	Nascimento et al. (2015)
Leaves	Aqueous extract	Thiobarbituric acid (TBA) test, reducing power, DPPH and hydrogen peroxide	When compared with ascorbic acid (standard), the extract showed low antioxidant activity.	Alhaji et al. (2014)
Root, stem, leaf, whole plant	Methanolic, aqueous extract	Hydroxyl and superoxide radical scavenging, ferrous chelating activities	Aqueous and methanolic extracts of root, stem, leaf and whole plant showed antioxidant activity.	Sharma et al. (2014)
Leaves	Methanolic extract	Phosphomolybdenum assay, ferric reducing ability, hydroxyl radical scavenging, thiobarbituric acid reactive substance assay, metal ion-chelating capacity	The extract exhibited significant antioxidant and free radical-scavenging activity.	Phatak and Hendre (2015a)
Leaves	Aqueous, methanolic and methanolic 50% extracts	DPPH, β-carotene-linoleate method, metal (ferrous ion) chelating method, lipid peroxidation inhibition; electron paramagnetic resonance spectroscopy, inhibition of DNA breakage activity, browning potential, tyrosinase inhibition assay	The methanolic 50% extract was the most active. The study indicated that the extracts can be a potent antioxidant. And they were active against the tyrosinase.	Gupta et al. (2015)
Leaves	Methanolic extract	DPPH scavenging, reducing power, and hydroxyl radical scavenging assay	DPPH radical, hydroxyl radical and reducing power assays showed IC50 values of 25.31 ± 0.34, 55.94 ± 0.68 and 11.18 ± 0.74 μg/ml, respectively.	Mabeku et al. (2017)
Leaves	Hydroethanolic 70%	DPPH scavenging method	The extract presented antioxidant activity.	Hara et al. (2018)

Box 7: Continued

Plant part	Extract/fraction/compound	Method	Result	Reference
Immunomodulatory activity				
Leaves	Aqueous extract	Mast cell degranulation in mesentery and histamine release assay	The extract prevented the mast cell degranulation antigen-induced, at 100 μg/ml for 30 min, and the histamine release at 0.5 mg/ml for 1 h.	Cruz et al. (2008)
Leaves	Aqueous extract, isolated compounds	Effect of Kp, flavonoid quercetin (QE), quercitrin (QI) on mast cell activation	Treatments with Kp and QE inhibited degranulation and cytokine production of bone marrow-derived mast cells following IgE/FcεRI crosslinking. Treatment with Kp significantly reduced levels of TNF in supernatant.	Cruz et al. (2012)
Antiproliferative activity				
Leaves	Ethanolic extract, acid fraction	Evaluation in lymphocytes of mice BALB/c inguinal lynphonodes and human peripheral blood	The acid fraction was 20 times more effective then the ethanolic extract in inhibiting lymphocyte proliferation.	Almeida et al. (2000)
Thombolytic activity				
Whole plant	Methanolic extract	Method of Prasad	The extract presented moderate thrombolytic activities (16.41%).	Sharker et al. (2012)
Treatment of the overactive bladder syndrome				
Leaves	Juice	Strips of porcine detrusor were prepared in Krebs solution and contractility was measured	The juice extract inhibited contractions induced by electrical field stimulation and relaxes carbachol-induced contractions.	Schuler et al. (2012)
Leaves	Methanolic extract	Detrusor muscles trips were prepared from porcine bladder sand, the electrically induced muscle contractility measured	At 10% concentration, the extract reduced the contractility of the detrusor to 58.6 ± 13.3% after 74 min, after a dose-independent initial increase in contractility during the first 40 min.	Fürer et al. (2015)
Leaves	Juice	Detrusor muscles trips were prepared from porcine urinary bladders	The pretreatment increased contraction strength of porcine detrusor strips relative to the negative control.	Bachamann et al. (2017)
Antiurolithic activity				
–	Ethanolic extract	Crystallization of calcium oxalate crystals	The extract has antiurolithic activity and has the ability in reduced the size of crystals.	Yasir and Waqar (2011)
Leaves	Aqueous extract	Nucleation assay (turbidity method), aggregation assay	The extract had greater capacity to dissolve calcium oxalate. The extract inhibited the crystallization. The extract was slightly better in comparison to Cystone (standard) in inhibiting the formation of COD crystals.	Phatak and Hendre (2015b)
Tocolysis activity				
Leaves	Aqueous extract	Contractility was measured in strips of term myometrium exposed to increasing concentrations of *B. pinnatum*	Inhibition of spontaneous contraction was concentration-dependent. The extract increased contraction frequency by 91% and inhibited oxytocin-stimulated contractions by 20% with slightly decreased frequency.	Gwehenberger et al. (2004)
–	Juice	Stimulation by oxytocin activity	The juice prevented the oxytocin-induced increase in $[Ca^{2+}]_i$ in human myometrial cells in a dose-dependent manner, reaching a *ca.* 80% inhibition at a 2% concentration.	Simões-Wüst et al. (2010)
Leaves	Leaf press juice (BPJ)	Repeated addition of BPJ in several dilutions (undiluted, 1–10%) on myometrium strips	The BPJ decreased amplitude and inhibited contractility significantly faster and increased frequency significantly faster then the control.	Wächter et al. (2011)
Anticancer activity				
Leaves	Bufadienolides of methanolic extract	Inhibitory effect on early antigen of Epstein–Barr virus in the induction Raju cell activation by a tumor promoting gene	All bufadienolides showed inhibitory activity and briofilin A exhibited the highest activity (IC_{50} = 0.4 μM) among the compounds. Thus, bufadienolides are potential cancer chemopreventive agents.	Supratman et al. (2001)
Leaves	Chloroform extract	MTT, electrophoretic mobility shift, northern blotting and assays in cervical cancer cells	The extract inhibited cervical cancer cell growth by 30%. Results shown depict a dose-dependent decrease in the level of HPV18 transcripts in cells treated with crude extract.	Mahata et al. (2012)
Antimutagenic activity				
Leaves	Ethyl acetate, methanol, petroleum ether extracts	Antimutagenic activity against EMS (ethyl methanosulfonate)-induced reversion mutations in *S. typhimurium*	The ethyl acetate and petroleum ether extracts exhibited potent antimutagenic activities at the non-toxic concentrations of 200 and 400 μg/plate.	Obaseiki-Ebor et al. (1993)

Box 7: Continued

Plant part	Extract/fraction/compound	Method	Result	Reference
Leaves	Juice	*Salmonella/mammalian* microsome assay (Ames test)	At a dose 0.25 mg/ml, the juice caused a statistically significant reduction in the mutagenicity of 2AA ($p \leq 0.05$) and the percent of inhibition was more then 90% at higher doses in all conditions tested.	Umbuzeiro-Valent et al. (1999)
Hepatoprotective activity				
Leaves	Juice, ethanolic extract	Isolation of hepatocytes and examination of the effect of toxicants along with the test samples	The concentrate and ethanolic extract significantly decreased the GOT (glutamyl oxalacetic acid transaminase) level by 55.55 and 36.50% and GPT (glutamyl pyruvate transaminase) level by 69.57 and 38.61%, respectively.	Yadav and Dixit (2003)
Acetylcholinesterase activity				
Leaves	Ethyl acetate, methanol extracts	Microplate assay to AChE inhibitory activity and positive and false positive activity in TLC	The ethyl acetate extract showed a strong inhibition of acetylcholinesterase activity.	Feitosa et al. (2011)
Antidiabetic activity				
Stalk	Aqueous, ethanolic extracts	α-Amylase inhibition	The ethanol extract showed significant inhibitory activity of α-amylase enzyme in relation to the aqueous extract.	Matthew et al. (2013a)
Phospholipase A_2 activity				
Leaves	Hydroethanolic 50% extract	Phospholipase A_2 activity was determined turbidimetrically in 96-well microplates using an egg yolk suspension	The extract showed significant inhibitory activity of PLA_2.	Fernandes et al. (2016)

Box 8: Non-clinical *in vivo* studies performed for *Bryophyllum pinnatum*.

Plant part	Extract/fraction/ compound	Dose and route	Method	Animal model	Result	Reference
Gastroprotective activity						
Leaves	Methanolic extract	100, 300 mg/kg, *i.p.*	Ulcer induced by indomethacin, serotonin, reserpine, acetic acid ethanol and stress; Lesion gastric in pylorus-ligated induced by acetylsalicylic acid, Duodenal ulcers induced by histamine	Charles-Foster rats, albino guinea pigs	The extract exhibited a significant inhibitory effect on aspirin-induced ulcers. Pretreatment at 300 mg/kg inhibited the formation of indomethacin-induced gastric ulcers. There was a significant inhibitory effect on ulcer formation by serotonin and reserpine. The extract protected against of ulcers by stress. The extract reduced the severity of ulcers and caused a significant reduction of ulcer index in the ethanol-induced ulcers.	Pal and Chaudhuri (1991)
Leaves	Methanolic extract	10, 20, 40 mg/kg of aqueous extract	Indomethacin induced gastric ulceration	Adult male albino Wistar rats	The extract had a dose-dependent gastro-protective effect on indomethacin induced ulceration. With results, the extract could probably be more potent then propranolol in the measured variables.	Adesanwo et al. (2007)
Leaves	Aqueous extract	1 and 2 g/kg, oral	Gastric lesion induced by indomethacin	Male Wistar rats	The aqueous extract showed significant anti-ulcerogenic effect when compared with the negative standard. The ranitidine and aqueous extract at 1 and 2 g/kg reduced the ulceration in 45.49%, 49.51%, respectively.	Braz et al. (2013)
Whole plant	Aqueous extract and mucilage	500 and 750 mg/kg	Ulcer induced by ethanol	Female Wistar rats	The extract at dose of 750 mg/kg *p.o.* and mucilage at dose of 500 mg/kg *p.o.* markedly decrease the incidence of ulcers in rats. There was a decrease in the gastric volume, free and total acidity and ulcerative index was 72.69 for extract and 69.65% for mucilage.	Sharma et al. (2014)

Box 8: Continued

Plant part	Extract/fraction/ compound	Dose and route	Method	Animal model	Result	Reference
Leaves	Aqueous extract	125, 250, 500 mg/kg, oral	Gastrics lesions induced by ethanol and indomethacin	Female Wistar rats	The pre-treatment with protects the mucosa of rats against the gastric damage of indomethacin and ethanol-induced gastric lesions, and significantly reduced damage by improving parameters related to oxidative stress and inflammation on mucosal structures.	Araújo et al. (2018)
Helicobacter pylori *activity*						
Leaves	Methanolic extract	125, 250, 500 mg/kg, oral	Inoculation of *H. pylori* in mice	Swiss mice	The extract showed a significant anti-*Helicobacter* activity and reduced *H. pylori* colonization of gastric tissue from 100% to 17%.	Mabeku et al. (2017)
Anti-inflammatory activity						
Leaves	Aqueous extract	25–800 mg/kg, oral	Fresh egg albumin-induced paw edema	Young adult Wistar rats	The extract produced dose- and time-related, significant reductions in the fresh egg albumin-induced acute inflammation in the rat hind paw.	Ojewole (2005)
Leaves	Methanolic extract	500 mg/kg, *i.p.*	Paw edema induced by formaldehyde in rats	Sprague Dawley rats and Swiss albino mice	Significant activity was observed at the third hour after carrageenan injection, with 72.64% reduction in paw volume.	Gupta et al. (2009)
Leaves	Aqueous extract (AE), esteroidal derivative (ED)	400 mg/kg (AQ); 300 mg/kg (ED), oral	Carrageenan induced rat paw edema method	Wistar albino rats	The AE and ED were active in reducing inflammation (87.29 and 84.45% respectively) somewhat less then diclofenac.	Afzal et al. (2012)
Leaves	Ethanolic extract	0.1, 0.5, 1.0 mg/ear in 20 ml of acetone, topically applied on the right ear	Ear edema induced by croton oil, arachidonic acid (AA), phenol and ethyl phenylpropiolate (EPP), capsaicin.	Male Swiss albino mice	The topical application of extract (0.5 and 1 mg/ear) significantly inhibited the croton oil induced mice ear edema as well as the edema caused by AA, phenol, capsaicin and EPP.	Chibli et al. (2014)
Flowers	Aqueous extract	3, 10, 30 mg/kg, subcutaneously	Croton oil-induced mice ear edema	Adult male Swiss mice (25–35 g)	Extract produced a dose-related antiedematogenic effect evidenced by the reduction in croton oil-induced mice ear edema by 50.8, 54.2, and 64.4%, respectively.	Ferreira et al. (2014)
Flowers	Aqueous extract	300 mg/kg, subcutaneously	Carrageenan-Induced Pleurisy	Adult male Swiss mice (25–35 g)	The pretreatment with extract or dexamethasone reduced the leukocyte migration into the pleural cavity by 56.1 and 43.9%, respectively. The pretreatment reduced the TNF-α concentration in pleural exudates by 44.7 and 69.8%, respectively.	Ferreira et al. (2014)
Immunomodulatory activity						
Leaves	Aqueous extract	400 mg/kg by gavage; 200 mg/kg, *i.p.*	Shock anaphylactic model	Male BALB/c mice and Lou-M rats	Oral protection was accompanied by decreased production of OVA specific IgE antibodies, reduction of eosinophilia, and decreased production of IL-5, IL-10 and TNF-α.	Cruz et al. (2008)
Leaves	Aqueous extract	400 mg/kg by intragastric	Airway allergic disease model	BALB/c mice	The extract decreased the development of hyporesponsiveness airway, metaplasia and caliciform cells and IL-5, IL-5 and TNF production.	Cruz et al. (2012)

Box 8: Continued

Plant part	Extract/fraction/ compound	Dose and route	Method	Animal model	Result	Reference
Wound healing potential						
Leaves	Petroleum ether, alcohol, water extracts	400 mg/kg, oral	Resutured incision wound, dead space wound, excision wound	Albino rats	All the three extracts showed significant increase in the breaking strength of incision wound. Water extract showed significant increase in wound contraction and formation of scars on 17th post wounding day.	Khan et al. (2004)
Leaves	Ethanolic extract	100 mg/kg, topical	Excision wound model	Male Sprague Dawley rats	On the 11th day post-wounding, there was a significant increase in the wound-healing activity. Progressive reduction in the wound area of the extract treated animals was observed by day 11 (86.3%).	Nayak et al. (2010)
Leaves	Aqueous extract wild-type and transgenic	1 ml of extract, topical	A purulent infection was modeled in rat and infected with *S. aureus* and *P. aeruginosa*	Adult male Wistar rats	The transgenic extract exhibits favorable effect on healing of wounds infected with *S. aureus* and with a combination of *S. aureus* with *P. aeruginosa*. The extract not transgenic was active, but not as the transgenic ones.	Lebedeva et al. (2017)
Leaves	Aqueous extracts of wild-type and transgenic plant	1 ml of extract, topical	After wounding, the rats were infected with *C. albicans*	Adult male Wistar rats	The transgenic extract exhibits favorable effect on healing of wounds infected with *C. albicans*.	Zakharchenko et al. (2017)
Bronchospasmolytic effects/effects on the contractile responses/anti-asthmatic and antitussive properties						
Leaves	Aqueous extract	200 mg/kg/day and 400 mg/kg/day, oral	Effects on the contractile responses of isolated tracheal rings	Adult guinea pigs	The extract did not relax histamine or carbachol-induced precontractions. The presence of the extract in organ baths significantly reduced the maximal contractile response to cumulative concentrations of histamine or carbachol irrespective of the experimental group. The aqueous extract exhibited antispasmodic effects on the guinea pig tracheal rings.	Ozolua et al. (2010a)
Leaves	Aqueous extract	200, 400 mg/kg/day	Phenol red expectorant method (antitussive effects)	Adult guinea pigs	The extracts significantly increased the time for guinea pigs to experience preconvulsive dyspnea; reduced muscus viscosity in the sensitized group. Both doses also significant reduced the bouts of cough but only 400 mg/kg/day inhibited the amount of phenol red secretion.	Salami et al. (2013)
Leaves	Aqueous extract	0.001, 0.01, 0.1, 1, 10 mg/ml	Reduce the force of smooth muscle contraction of isolated guinea pig trachea chains induced by acetylcholine or histamine	Adult guinea pigs	The effect of the extract on the acetylcholine-induced force of contraction was apparent at 10 mg/ml and involved a decrease of approximately 50% when compared to that produced by acetylcholine 3×10^5 M alone.	Mans et al. (2015)
Analgesic activity						
Leaves	Aqueous extract (AE), esteroidal derivative (ED)	400 mg/kg (AQ); 300 mg/kg (ED), oral	Acetic acid induced writhing in mice	Swiss albino male mice	ED is possessing a significant analgesic activity when compared with a standard drug showing 75.72% of protection as compared to that of aqueous extract of *B. pinnatum* and diclofenac (100 mg/kg, *i.p.*).	Afzal et al. (2012)

Box 8: Continued

Plant part	Extract/fraction/ compound	Dose and route	Method	Animal model	Result	Reference
Action on the gabaergic system						
Leaves	Juice	4.0 g/kg, *i.p.*	Measure potentiation "sleeping-time" induced by benzodiazepines and seizure threshold measure	Wistar male rats of 220–250 g	The juice had no effect on the GABAergic system in rats in working conditions.	Agostinho et al. (1992)
Antinociceptive activity						
Leaves	Aqueous extract	25, 50, 100, 200, 400, 800 mg/kg *i.p.*	'Hotplate' (thermal) and 'acetic acid' (chemical) test	BALB/c albino mice	The extracts (50–800 mg/kg *i.p.*) produced significant antinociceptive effects against thermally- and chemically induced nociceptive pain stimuli.	Ojewole (2005)
Leaves	Methanolic extract	100, 200, 400 mg/kg body weight), oral	Acetic acid-induced gastric pain model	Male Swiss albino mice	The extract demonstrated a significant dose-dependent reduction in the number of writhings. The highest inhibition of writhings was observed at a dose 400 mg/kg.	Morshed et al. (2010)
Flowers	Aqueous extract	30, 100, 300 mg/kg, subcutaneous	Acetic acid-induced abdominal writhing	Swiss mice	Pretreatment of mice with extract at 100 and 300 mg/kg produced antinociception evidenced by the reduction of the number of acetic acid-induced writhings by 30.1% and 70.1%, respectively, and extract (30 mg/kg) was ineffective.	Ferreira et al. (2014)
Anticonvulsant activity						
Leaves	Extraction with saline solution	50, 100, 200 mg/kg, oral	Strychnine- and picrotoxin-induced convulsion	Swiss mice	Treatment caused a dose-related delay of the onset to tonic convulsion caused by strychnine and picrotoxin. Even if it was unable to prevent convulsion, an inhibition of mortality was also observed with 100 and 200 mg/kg.	Yemitan and Salahdeen (2005)
Roots, stem	Methanolic extracts	100, 200, 400, 800 mg/kg, oral	Induction of seizures by pentylenetetrazole model	BALB/c mice	The extract exhibited a dose-dependent increase in latency to myoclonus, clonus, and tonic–clonic seizures, acting similar to diazepam and offering 100% protection against the lethal effects of pentylenetetrazol.	Mora-Pérez and Hernández-Medel (2016)
Locomotor activity						
Leaves	Aqueous extract (Juice)	4.0 ml/kg	Avoidance active two-way	Male Wistar rats	The juice significantly increased the percentages of avoidance (90.30 ± 7.60%) and leakage (9.36 ± 1.78%) of the animals observed.	Nassis et al. (1995)
Stems	Ethanolic, aqueous extract	300, 600 mg/kg, v.o.	Evaluate the CNS-depressant activity of extracts on the locomotor activity	Swiss albino mice	The ethanolic extract showed a higher CNS-depressive activity in comparison to aqueous extract, but similar effect to the standard drug (chlorpromazine).	Matthew et al. (2013b)
Neurosedative activity						
Leaves	Extraction with a saline solution	50, 100, 200 mg/kg, oral	Pentobarbitone-induced sleep, Hole-board method and Evasion test	Swiss mice	The aqueous extract produced significant CNS depressant effects. It produced a significant and dose-related prolongation of the onset and duration of the sleeping time on pentobarbitone-induced hypnosis, and a reduction in head-dip and an increase in percentage of mice remaining in box in the head-dip and evasion tests.	Yemitan and Salahdeen (2005)

Box 8: Continued

Plant part	Extract/fraction/ compound	Dose and route	Method	Animal model	Result	Reference
Muscle relaxant activity						
Leaves	Extraction with a saline solution	50, 100, 200 mg/kg, oral	Chimney test, Traction test, climbing and inclined screen test	Swiss mice	A loss of muscle coordination in the inclined screen, traction and climbing tests, and in the chimney test were observed.	Yemitan and Salahdeen (2005)
Hepatoprotective activity						
Aerial parts	Ethanolic, aqueous extracts	250, 500 mg/kg, oral	Injury hepatic induced by DENA	Wistar albino male rats	The ethanolic extract had no significant effect in the parameters. The dose of 500 mg/kg of ethanolic extract significantly increased SGPT and ALP level. Treatment with both doses of aqueous extract significantly reversed the parameters at a dose-dependent manner.	Afzal et al. (2013)
Leaves	Juice, ethanolic extract	200 mg/kg, intraperitoneal	CCl_4-induced hepatotoxicity	Albino Wistar rats of either sex (75–150 g)	Juice concentrate decreased the SGOT, SGPT, SALP and SBLN levels by 51.69, 92.47, 72.50 and 105.50%, respectively. Ethanolic extract decreased the same levels by 29.45, 81.37, 45.82 and 49.00%.	Yadav and Dixit (2003)
Antileishmania activity						
Leaves	Aqueous extract	Oral: 4 and 8 mg; *i.v.*: 2 mg; *i.p.*; topic: 50 μl	Limiting dilution assay, delayed-type hypersensitivity (DTH) reaction and antibody production	Male BALB/c mice	The oral treatment significantly delayed disease onset. When started in the early stages of infection, daily oral dose of 8/0.2 mg/ml prevented growth of the lesion and the effect was long lasting, accompanied by a significant reduction in the number of viable parasites.	Silva et al. (1995)
Leaves	Aqueous extract	400 mg/kg by gavage	Visceral leishmaniasis, using the *Leishmania chagasi* infection in mice	Female BALB/c mice	The extract prevented parasite growth in both the spleen and the liver, reduced levels of IgG parasite specific serum and decreased ability of spleen cells to produce IL-4, but not IFN-c and nitric oxide.	Gomes et al. (2009)
Leaves	Aqueous extract, isolated flavonoids	Oral, 320 mg/kg/day to extract and 16 mg/kg/dia.	Antileishmania activity in mice infected with *L. amazonensis*	BALB/c mice	All treatments had controlled the growth of the lesion caused by *L. amazonensis* and significantly reduced parasitic load. These flavonoids were as effective as crude aqueous extract at dose 320 mg/kg.	Muzitano et al. (2009)
Antimalarial activity						
Aerial part	Hydroethanolic 70% extract	100, 250, 500, 1000 mg/kg/day	Antimalarial activity	Rodent malaria *Plasmodium vinckeipetteri*	The extract presented an intermediary activity by inhibiting 63% of the parasite growth at 1000 mg/kg.	Muñoz et al. (2000)
Antihypertensive activity						
Leaves	Aqueous extract	12.5, 25.0 mg/kg body weight, *i.v.*	Blood pressure determination	Cats	The dose of 12.5 mg/kg produced a slight reduction in the blood pressure by 3–4 mmHg. At 25.0 mg/kg, the fall in the blood pressure was still slight; it reduced by 8–9 mmHg. The extract given to the cat was increased to 37.5 mg/kg and the fall in blood pressure was between 8 and 12 mmHg. 50 mg/kg reduced the blood pressure more markedly by 8–15 mmHg.	Ghasi et al. (2011)

Box 8: Continued

Plant part	Extract/fraction/ compound	Dose and route	Method	Animal model	Result	Reference
Leaves	Aqueous extract	25 mg/kg/day, 50 mg/kg/day or 100 mg/kg/day by, gavage	Extract effect on blood pressure in normotensive and hypertensive rats (NaCl 18% for 4 weeks)	Male albinos Wistar rats	The extract significantly prevented the increase in systolic and diastolic blood pressure in rats with high level of salt. The co-administration of 25, 50 and 100 mg/kg/day, significantly decreased the blood pressure at 32, 24 and 47% (PAS) and 35, 33 and 56% (for DBP) respectively. No significant changes were reported for cardiac frequency.	Bopda et al. (2014)
Antidiabetic activity						
Leaves	Aqueous extract	25, 50, 100, 200, 400, 800 mg/kg, oral	Streptozotocin (STZ)-induced diabetes mellitus	Young adult Wistar rats	Pre-treatment of the fasted rats with relatively moderate to high doses aqueous extract produced significant reductions in the blood glucose concentrations of both fasted normal and fasted diabetic rats.	Ojewole (2005)
Leaves	Ethanolic extract	500 mg/kg	Streptozotocin-induced diabetic rats	Wistar strain albino rats	The postprandial test results showed that the plant extract exerted some hypoglycaemic effects on the blood glucose level in the fasting normal rats.	Ogbonnia et al. (2008)
Stalk	Aqueous and ethanolic extracts	300, 600 mg/kg, oral	Diabetes I Alloxan-induced	Wistar rats	The extracts had a good hypoglycemic and antihyperglycemic activity.	Matthew et al. (2013a)
Leaves	Aqueous extract	Oral: 200, 400 and 800 mg/kg and glybenclamide 2 mg/k + 800 mg/kg of extract	Diabetes induced by D-glucose	Albino rats	The extract decreased the glucose level after 120 min administration. The dose of 200 mg/kg showed significant decrease in the glucose level compared to the other doses performance. The association of glybenclamide promoted the major decreased in the glucose level.	Aransiola et al. (2014)
Leaves	Aqueous extract	3 mature leaves ~9.96 g/70 kg or about 0.14 g/kg	Streptozotocin-induced diabetic rats	Adult Sprague rats	There was a decreasing trend in the average food intake among the groups (normal group > diabetic group > treated diabetic group.	Menon et al. (2015)
Leaves	Aqueous extract	3 mature leaves ~9.96 g/70 kg or about 0.14 g/kg	Streptozotocin-induced diabetic rats	Adult Sprague–Dawley rats	There was weight loss and reduced food consumption in the treated diabetic group. Serum glucose levels were reduced. Serum catalase activity was significantly increased in the treated diabetic group. There was a significant increase in Mg ATPase activity.	Menon et al. (2016)
Hypocholesterolemic activity						
Leaves	Ethanolic extract	500 mg/kg	Evaluation of hypolipidaemic effects in animals treated with extract for 21 days	Wistar strain albino rats	The extract clearly demonstrated the presence hypolipidemic agents in the extract. There was also a significant decrease in both triglyceride and LDL cholesterol levels while significant increase in HDL cholesterol levels.	Ogbonnia et al. (2008)
Leaves	Aqueous extract	3 mature leaves ~9.96 g/70 kg r about 0.14 g/kg	Streptozotocin-induced diabetic rats	Adult Sprague rats	There was a significant elevation in triglyceride level in the diabetic group, which was reduced toward normal level by the treatment. Total cholesterol level was also elevated in the diabetic group and there was a decreasing trend toward the normal group by the treatment. Additionally, HDL cholesterol was significantly reduced.	Menon et al. (2015)

Box 8: Continued

Plant part	Extract/fraction/ compound	Dose and route	Method	Animal model	Result	Reference
Hormonal activity						
Leaves	Aqueous extract (Juice)	4.0 mg/kg, s.c.	Effects on the release of gonadotropins	Wistar rats	The rats that received the juice showed lordosis coefficient (sexual receptivity) higher then the control group. It was observed a significancy for latency to ejaculation treated animals compared to control.	Nassis et al. (1996)
Effect on hematological parameters						
Leaves	Methanolic extract	100, 200, 400, 600 mg/kg, oral	Animals were treated with extracts at the doses once daily during 28 days	Adult male Wistar rats	Hemoglobin, packed cell volume and total white blood cell of all treated rats were increased. The platelet count was decreased in all treated groups but only in group A (100 mg/kg). The blood film report revealed normocytic and normochromic red blood cells.	Ufelle et al. (2011)
Nephroprotective activity						
Leaves	Aqueous extract	125 mg/kg/day, *i.p.*	Nephrotoxicity induced by gentamicine at the dose 100 mg/kg/day during 8 days	Male albino Wistar rats	The extract protects rat kidneys from gentamicin-induced histopathological changes. This extract also normalized the gentamicin-induced increases in urine and plasma creatinine, blood urea and blood urea nitrogen levels.	Harlalka et al. (2007)
Leaves	Aqueous extract	25 and 50 mg/kg, oral for 14 days	Nephrotoxicity induced by CCl_4 *i.p.* during 7 days	Albino Wistar rats	The pre-treatment with the two doses inhibits arginase II preventing renal oxidative damage occasioned by CCl_4. In addiction reduced endothelial NO, functional SH groups, oxidative enzymatic antioxidant status and normalizing the histological architecture of the kidney.	Anadozie et al. (2018)
Antilithic activity						
Leaves	Ethanolic and hydroethanolic 70% extracts	100, 200, 400 mg/kg, oral	Renal calculi induced by ethylene glycol	Male albino Wistar rats	The extracts attenuated the EG-induced decrease in body weight and elevation in urinary parameters and serum biochemical parameters. Also decrease in urine volume, pH, magnesium and creatinine clearance, oxidative and histological damages in kidneys.	Yadav et al. (2016)
Adjuvant treatment to poisoning (local anti-inflammatory activity)						
Leaves	Hydroethanolic 50% extract	125, 250, 500 mg/kg, *i.p.*	Paw edema and hemorrhagic activity induced by *Bhotrops jararaca*	Swiss albino mice	In the pre-treatment protocol, the extract reduced the hemorrhagic activity reaching about 40% and in the post-treatment protocol about 30%. In the antiedematogenic activity, *B. pinnatum* was active inhibiting about 66% and 30% in pre and post-treatment protocols, respectively.	Fernandes et al. (2016)

metabolites of the leaves juice may inhibit detrusor contractility (Bachamann et al., 2017), supporting the previous clinical study.

Toxicology

Acute toxicity of *K. laciniata* species has been investigated in various types of extracts made from leaves or the whole plant. On the other hand, the toxicological studies involving *B. pinnatum* were performed mainly with extracts of the leaves. The *in vitro* and *in vivo* toxicity assays reported in the literature for *K. laciniata* and *B. pinnatum* species are shown in Boxes 9 and 10, respectively.

Although most studies have shown that both species present low toxicity and good safety, one study observed some reactions to the central nervous system attributed to *K. laciniata*, as well as spasms, tachycardia, fine and coarse tremors and aggression (Silva, 2007). Other study reported a reduction in the sensitiveness of the rats to noise and touch, which also presented jerkiness and lethargy (Fondjo et al., 2012). For *B. pinnatum*, some studies have reported cytotoxicity (Sowemimo et al., 2007; Abdellaoui et al., 2010; Biswas

Box 9: Non-clinical *in vitro* and *in vivo* toxicity studies reported for *Kalanchoe laciniata*.

Plant part	Extract	Dose and rout	Method	Result	Reference
In vitro toxicity					
Leaves	Methanolic extract	–	Cytotoxicity against human carcinoma cells	*K. crenata* showed good cytotoxicity activity against mesothelioma, lung and breast cancer cells, but the best activity was against mesothelioma. The extract induced apoptosis *via* ROS production.	Kuete et al. (2017)
Whole plant	Methanolic 70% and hexane extract	–	Genotoxic potential using Ames assay (*Salmonella typhimurium*) and cytotoxicity was evaluated using MTT assay	The methanolic and *n*-hexane extracts exhibited significant mutagenicity and cytotoxicity.	Sharif et al. (2017)
In vivo toxicity					
Leaves	Aqueous 1 (before flowering) and aqueous 2 (after flowering)	0.25–5 g/kg, *i.p.*	Acute toxicity using Swiss mice	No toxicity was observed within 48 h of administration.	Mourão et al. (1999)
Leaves	Hydroethanolic extract (90%)	1000–3000 mg/kg, *i.p.*	Acute toxicity using Swiss mice	The LD_{50} was 1925 mg/kg and numerous reactions to central nervous system level to escape reactions, spasms, tachycardia, fine and coarse tremors, aggression, among others were observed.	Silva (2007)
Whole plant	Water–ethanol extract	0.2, 0.4, 0.8, 1.5, 3, 5 g/kg, oral	Acute toxicity using male Wistar rats	Neither mortality nor gross behavior change was observed at different doses up to 5 g/kg.	Kamgang et al. (2008)
Leaves	Hydroethanolic extract (50%)	250 mg/kg, gavage	Mutagenicity: micronucleus assay *in vivo* in mouse bone marrow using mice	A mutagenic effect of the extract was observed. However, more studies are necessary to prove and evaluate the effects.	Paiva and Batitucci (2008)
Whole plant	Methanol extract	2, 4, 6, 8, 10 g/kg, oral	Acute toxicity using male Wistar rats	The doses 4, 6, 8 and 10 g/kg reduced the sensitiveness of rats to noise and touch, which also showed jerkiness and lethargy, and induced soft feces and 66% mice death within 30 min of administration. The 10 g/kg dose caused 100% mice death. The LD_{50} was 4.4 g/kg.	Fondjo et al. (2012)
Leaves	Hydroethanolic extract (50%)	250, 500, 1000, 2000 mg/kg, gavage	Acute toxicity and subchronic toxicity using Swiss mice Swiss mice	The extract showed low acute and subchronic *in vivo* toxic effects. The biochemical parameters were not affected and there were no significant hematologic changes between the groups studied. The extract showed slight liver changes at doses 500 and 1000 mg/kg through the liver enzymes linked to the hepatic histopathology, as a characteristic sign extract metabolism.	Fonseca (2014), Fonseca et al. (2018)

Box 10: Non-clinical *in vitro* and *in vivo* studies reported for *Bryophyllum pinnatum*.

Plant part	Extract	Dose and route	Method	Result	Reference
In vitro toxicity					
Whole plant	Ethanolic extract (80%)	–	Brine shrimp lethality test and standard telomerase elongation assay *TRAP (telomere repeat amplification protocol)*	LD_{50} values of extracts with ≤100 mg/ml was considered active and those with <20 were considered very active.	Sowemimo et al. (2007)
Stalks, leaves, flowers	Ethanolic extract	–	Cytotoxicity against six cell lines	Non-cytopathogenic effect at concentrations between 2 and 5%.	Gonçalves et al. (2009)
Leaves	Methanolic extract	–	Cytotoxicity in keratinocytes for 48 h	The extract had strong cytotoxicity, because the viability of keratinocytes is fully recovered only for the extract at lower concentrations (≤0.78 mg/ml).	Abdellaoui et al. (2010)
Leaves, stems	Petroleum ether, aqueous extracts	–	Brine shrimp lethality bioassay	Both extracts exhibited lethality against the brine shrimp nauplii. The respective LC_{50} and LC_{90} of the petroleum ether (25.12 and 177.83 μg/ml) and aqueous extract (25.12 and 173.78 μg/ml) were assessed.	Chowdhury et al. (2011)
Leaves	Chloroform extract	–	Brine shrimp lethality bioassay	Moderate level of general toxicity in the brine shrimp lethality bioassay (LC_{50} 125.89 and LC_{90} 234.42 μg/ml) was observed.	Biswas et al. (2012)
Leaves	Hexane, dichloromethane, ethanolic extract	–	MTT assay	The extracts exhibited potential *in vitro* cytotoxicity against the four human cell lines tested.	Kaewpiboon et al. (2012)
Leaves	Aqueous, ethanolic, methanolic extract	–	MTT assay in BHK assay; and neutral red assay (cytotoxicity)	The aqueous and ethanolic extracts showed better responses compared to the methanolic one. The concentration of 10 mg/ml of the ethanolic extract inhibited the cancerous growth.	Joshi and Chauhan (2013)
In vivo toxicity					
Leaves	Aqueous extract	16 mg/0.2 ml PBS/day; 30 days	Normal BALB/c mice received 16 mg the gavage for 30 days	Absence of chronic toxicity to the liver, heart or kidney.	Torres-Santos et al. (2003)
Whole plant	Ethanolic extract (80%)	10, 100, 1000 μg/ml	Brine shrimp lethality test	*Bryophyllum calycinum* was considerably toxic and consistent with the brine shrimp results.	Sowemimo et al. (2007)
Leaves	Methanolic, aqueous extracts	350–2600 mg/kg methanolic and aqueous; 500–3000 mg/kg methanolic, *i.p.*	Swiss albino male mice and rats, *i.p.*, with graded doses. The methanolic and aqueous extracts were also administered orally in graded doses in mice and rats to test their oral toxicity	The LD_{50} values of methanolic extract in mice and rats were 1159.03 and 1459.69 mg/kg, respectively, and the aqueous extract were 957.02 and 1064.21 mg/kg, respectively. The extracts were non-toxic orally in doses up to 3 g/kg body weight in mice and rats.	Devbhuti et al. (2008)
Leaves	Aqueous extract	1, 2, 3, 4, 5 g/kg, oral	Acute and sub-acute toxicological experiments in Sprague-Dawley rats	The oral LD_{50} of the extract was indeterminable as there were no deaths recorded and no obvious toxicological signs at 5 g/kg body weight. However, by the intraperitoneal route, the LD_{50} was estimated in 1.8 g/kg.	Ozolua et al. (2010b)
Leaves	Aqueous, ethanolic extracts	5, 50, 500, 2000 mg/kg, oral	Acute toxicity by OECD 420 using male Wistar rats	The extracts were safe up to a dose of 2000 mg/kg.	Afzal et al. (2013)
Leaves	Ethanolic extract	100, 200 mg/kg, oral	Effect of extract on microanatomy of male Wistar rat's testis for 8 weeks	The extract at the doses showed abnormalities in the animal's testis, as increasing numbers of intercellular spaces within the seminiferous epithelium, reduction and increase of the lumen, suggesting cell disintegration.	Akpantah et al. (2014)
Leaves	Ethanolic and hydroethanolic 70% extracts	2000 mg/kg, oral	Acute toxicity by OECD 423 using Male albino Wistar rats	No toxic symptoms or mortality or moribund stage observed with single acute limit dose level of 2000 mg/kg in any animal during 14 consecutive days.	Yadav et al. (2016)

et al., 2012; Kaewpiboon et al., 2012). In addition, abnormalities in the animal's testis were observed in one study (Akpantah et al., 2014).

Therefore, it seems likely to infer that *K. laciniata* and *B. pinnatum* are safe to use acutely but is necessary performed additional studies to investigate their sub-chronic and chronic toxicity.

Conclusion

Several studies related to the botanical, chemical, ethnopharmacological, pharmacological and toxicological aspects of *B. pinnatum* have been conducted. On the other hand, only few studies about the chemical and pharmacological aspects of *K. laciniata* species have been reported. Toxicological studies are scarce for both species. Therefore, when we consider the several traditional uses of *K. laciniata*, it becomes detrimental to scientifically evaluate the pharmacological properties that have been attributed to this species. Despite the various traditional uses and non-clinical pharmacological studies reported for *B. pinnatum* and *K. laciniata*, clinical studies are still scarce. More studies should be conducted in order to identify the specific compounds that are responsible for the reported pharmacological activities for both species. Finally, the information reported in this review may contribute to recognizing the importance of *K. laciniata* and *B. pinnatum* as important plant sources for alternative treatment of the several disorders herein reported.

Authors' contributions

JMF and LMC contributed in data collect, systematization of articles in boxes and drafter the first version of the paper. JMF and EMGL were responsible for drawn chemical structures and in chemical box. JMF contributed in drafter the final version of the paper and to critical reading of the manuscript. MFP and EPA contributed to critical reading of the manuscript. EPA was responsible for the revision of the English manuscript. SMZL was responsible for the project concept and, critical reading of the manuscript and supervision of this study. All the authors have read the final manuscript and approved the submission.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bjp.2019.01.012.

References

Abat, J.K., Mattoo, A.K., Deswal, R., 2008. *S*-Nitrosylated proteins of a medicinal CAM plant *Kalanchoe pinnata* – ribulose-1,5-biphosphate carboxylase/oxygenase activity targeted for inhibition. FEBS J. 275, 2862–2872.

Abdellaoui, S., Destandau, E., Tori, A., Elfakir, C., Lafosse, M., Renimel, I., André, P., Cancellieri, P., Landemarre, L., 2010. Bioactive molecules in *Kalanchoe pinnata* leaves: extraction, purification and identification. Anal. Bioanal. Chem. 398, 1329–1338.

Adesanwo, J.K., Raji, Y., Olaleye, S.B., Onasanwo, S.A., Fadare, O.O., Ige, O.O., Odusanya, O.O., 2007. Antiulcer activity of methanolic extract of *Bryophyllum pinnatum* in rats. J. Biol. Sci. 7, 409–412.

Afzal, M., Gupta, G., Kazmi, I., Rahman, M., Afzal, O., Alam, J., Hakeem, K.R., Pravez, M., Gupta, R., Anwar, F., 2012. Anti-inflammatory and analgesic potential of a novel steroidal derivative from *Bryophyllum pinnatum*. Fitoterapia 83, 853–858.

Afzal, M., Ahmad, K., Saleem, S., Kazmi, I., Anwar, F., 2013. Effect of *Bryophyllum pinnatum* Lam. on *N*-diethylnitrosamine induced hepatic injury in rats. Pharmacologia 4, 82–88.

Agarwal, K., Varma, R., 2015. Ethnobotanical study of antilithic plants of Bhopal district. J. Ethnopharmacol. 174, 17–24.

Agostinho, A.G., Freitas, A.L.P., Miaguchi, A.S., Pieralini, C., Sacco, P.C.N., Nassis, C.Z., 1992. Estudo da ação do suco extraído das folhas de *Bryophyllum calycinum*. Arq. Med. ABC 15, 14–18.

Aguiar, C.M., Alencar, S.M., Tsai, S.M., Park, Y.K., 2007. Transformações enzimáticas de flavonoides. Bol. Centro Pesqui. Process. Aliment. 25, 61–76.

Agyare, C., Spiegler, V., Sarkodie, H., Asase, A., Liebau, E., Hensel, A., 2014. An ethnopharmacological survey and *in vitro* confirmation of the ethnopharmacological use of medicinal plants as anthelmintic remedies in the Ashanti region, in the central part of Ghana. J. Ethnopharmacol. 158, 255–263.

Akihisa, T., Kokke, W.C.M.C., Tamura, T., Matsumoto, T., 1991. Sterols of *Kalanchoe pinnata*: first report of the isolation of both C-24 epimers of 24-alkyl-Δ^{25}-sterols from a higher plant. Lipids 26, 660–665.

Akinpelu, D.A., 2000. Antimicrobial activity of *Bryophyllum pinnatum* leaves. Fitoterapia 71, 193–194.

Akinsulire, O.R., Aibinu, I.E., Adenipekun, T., Adelowotan, T., Odugbemi, T., 2007. *In vitro* antimicrobial activity of crude extracts from plants *Bryophyllum pinnatum* and *Kalanchoe crenata*. Afr. J. Tradit. CAM 4, 338–344.

Akpantah, A.O., Obeten, K.E., Edung, E.S., Eluwa, M.A., 2014. The effect of ethanolic extract of *Bryophyllum pinnatum* on the micro anatomy of the testes of adult males Wister rats. Eur. J. Biol. Med. Sci. Res. 2, 37–44.

Albertasse, P.D., Thomaz, L.D., Andrade, M.A., 2010. Plantas medicinais e seus usos na comunidade da Barra do Jucu, Vila Velha, ES. Rev. Bras. Plantas Med. 12, 250–260.

Albuquerque, U.P., Monteiro, J.M., Ramos, M.A., Amorim, E.L.C., 2007a. Medicinal and magic plants from a public market in northeastern Brazil. J. Ethnopharmacol. 110, 76–91.

Albuquerque, U.P., Medeiros, P.M., Almeida, A.L.S., Monteiro, J.M., Lins Neto, E.M.F., Melo, J.G., Santos, J.P., 2007b. Medicinal plants of the *caatinga* (semi-arid) vegetation of NE Brazil: a quantitative approach. J. Ethnopharmacol. 114, 325–354.

Alhaji, U.I., Samuel, N.U., Aminu, M., Chidi, A.V., Umar, Z.U., Umar, U.A., Adewale, B.M., 2014. *In vitro* antitrypanosomal activity, antioxidant property and phytochemical constituents of aqueous extracts of nine Nigerian medicinal plants. Asian Pac. J. Trop. Dis. 4, 348–355.

Allorge-Boiteau, L., 1996. Madagascar centre de speciation et d'origine du genre *Kalanchoe* (Crassulaceae). In: Lourenço, W.R. (Ed.), Biogéographie de Madagascar. ORSTOM, Paris, pp. 137–145.

Almeida, C.C.S., Bogossian, F.B., Doi, A.P.K., Isoyama, D., Sih, G.H., Zanolla, W.R., Nassis, C.Z., 1997. Estudo da atividade antihistamínica da *Kalanchoe brasiliensis*. Arq. Med. ABC 1–2, 7–10.

Almeida, A.P., Silva, S.A.G., Souza, M.L.M., Lima, L.M.T.R., Rossi-Bergmann, B., Moraes, V.L.G., Costa, S.S., 2000. Isolation and chemical analysis of a fatty acid fraction of *Kalanchoe pinnata* with a potent lymphocyte suppressive activity. Planta Med. 66, 134–137.

Almeida, A.P., Muzitano, M.F., Costa, S.S., 2006. 1-Octen-3-*O*-α-*l* – *arabinopyranosymbeta*-glucopyranoside, a minor substance from the leaves of *Kalanchoe pinnata* (Crassulaceae). Rev. Bras. Farmacogn. 16, 485–489.

Amaral, A.C.F., Simões, E.V., Ferreira, J.L.P., 2005. Coletânea científica de plantas de uso medicinal. Fiocruz, Curitiba.

Anadozie, S.O., Akinyemi, J.A., Agunbiade, S., Ajuboye, B.O., Adewale, O.B., 2018. *Bryophyllum pinnatum* inhibits arginase II activity and prevents oxidative damage occasioned by carbon tetrachloride (CCl_4) in rats. Biomed. Pharmacother. 101, 8–13.

Anjoo, K., Saluja, A.K., 2010. Microscopical and preliminary phytochemical studies on aerial part (leaves and stem) of *Bryophyllum pinnatum* Kurz. Pharmacogn. J. 2, 254–259.

Anvisa, 2014. Resolução de Diretoria Colegiada n° 26 de 13 de maio de 2014. Dispõe sobre o registro de medicamentos fitoterápicos e o registro e a notificação de produtos tradicionais fitoterápicos. Ministério da Saúde, Agência Nacional de Vigilância Sanitária, http://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2014/rdc0026_13_05_2014.pdf (accessed January 2017).

Aoki, C., Hartati, S., Santi, M.R., Firdaus, R.L., Hanafi, M., Kardono, L.B.S., Shimizu, Y., Sudarmono, P., Hotta, H., 2014. Isolation and identification of substances with anti-hepatitis C virus activities from *Kalanchoe pinnata*. Int. J. Pharm. Pharm. Sci. 6, 211–215.

Aqil, F., Ahmad, I., 2003. Broad-spectrum antibacterial and antifungal properties of certain traditionally used Indian medicinal plants. World J. Microbiol. Biotechnol. 19, 653–657.

Aransiola, E.F., Daramola, M.O., Iwalewa, E.O., Seluwa, A.M., Olufowobi, O.O., 2014. Anti-diabetic effect of *Bryophyllum pinnatum* leaves. Int. J. Biol. Vet. Agric. Food Eng. 8, 95–99.

Araújo, E.R.D., Guerra, G.C.B., Araújo, D.F.S., Araújo, A.A., Fernandes, J.M., Araújo-Júnior, R.F., Silva, V.C., Carvalho, T.G., Ferreira, L.S., Zucolotto, S.M., 2018. Gastroprotective and antioxidant activity of *Kalanchoe brasiliensis* and *Kalanchoe pinnata* leaf juices against indomethacin and ethanol-induced gastric lesions in rats. Int. J. Mol. Sci. 19, http://dx.doi.org/10.3390/ijms19051265.

Arnason, T., Uck, F., Lambert, J., Hebda, R., 1980. Maya medicinal plants of San Jose Succotz, Belize. J. Ethnopharmacol. 2, 345–364.

Awortwe, C., Manda, V.K., Avonto, C., Khan, S.I., Khan, I.A., Walker, L.A., Bouic, P.J., Rosenkranz, B., 2015. *In vitro* evaluation of reversible and time-dependent inhibitory effects of *Kalanchoe crenata* on CYP2C19 and CYP3A4 activities. Drug Metab. Lett. 9, 48–62.

Bachamann, S., Betschart, C., Gerber, J., Furer, K., Mennet, M., Hamburger, M., Potterat, O., Mandach, U., Simões-Wust, A.P., 2017. Potential of *Bryophyllum pinnatum* as a detrusor relaxant: an *in vitro* exploratory study. Planta Med. 83, 1274–1280.

Bahekar, M., Kale, R., Nagpure, S., 2012. A review on medicinal plants used in scorpion bite treatment in India. Mintage J. Pharm. Med. Sci. 1, 1–6.

Bailon-Moscoso, N., Romero-Bonavides, J.C., Tinitana-Imaicela, F., Ostrosky-Wegman, P., 2015. Medicinal plants of Ecuador: a review of plants with

anticancer potential and their chemical composition. Med. Chem. Res. 24, 2283–2296.
Banzouzi, J.T., Koubemba, M.C.M., Prost, A., Mbatchi, B., Abena, A.A., 2008. Survey of analgesic plants used by tradipractitioners in Congo Brazzaville. Int. J. Bot. 4, 176–185.
Barroso, G.M., 1991. Sistemática de Angiosperma do Brasil. Imprensa Universitária, Minas Gerais.
Begossi, A., Hanazaki, N., Tamashiro, J.Y., 2002. Medicinal Plants in the Atlantic Forest (Brazil): Knowledge, Use, and Conservation. Hum. Ecol 30, 281–299.
Betschart, C., Mandach, U.V., Seifert, B., Scheiner, D., Peruchini, D., Fink, D., Geissbuhler, V., 2013. Randomized, double-blind placebo-controlled trial with *Bryophyllum pinnatum* versus placebo for the treatment of overactive bladder in postmenopausal women. Phytomedicine 20, 351–358.
Bhandary, M.J., Chandrashekar, K.R., Kaveriappa, K.M., 1995. Medicinal ethnobotany of the Siddis of Uttara Kannada district, Karnataka, India. J. Ethnopharmacol. 47, 149–158.
Bhat, P., Hegde, G., Hegde, G.R., 2012. Ethnomedicinal practices in different communities of Uttara Kannada district of Karnataka for treatment of wounds. J. Ethnopharmacol. 143, 501–514.
Bhat, P., Hegde, G.R., Hegde, G., Mulgund, G.S., 2014. Ethnomedicinal plants to cure skin diseases – an account of the traditional knowledge in the coastal parts of Central Western Ghats, Karnataka, India. J. Ethnopharmacol. 151, 493–502.
Bhatti, M., Kamboj, A., Saluja, A.K., Jain, U.K., 2012. *In vitro* evaluation and comparison of antioxidant activities of various extracts of leaves and stems of *Kalanchoe pinnatum*. J. Green Pharm. 6, 340–347.
Bhatti, M., Kamboj, A., Saluja, A.K., 2013. Spectrophotometric estimation of total polysaccharides in *Kalanchoe pinnatum* and *Kalanchoe crenata*. Int. J. Pharm. Pharm. Sci. 5, 40–41.
Biswas, S.K., Chowdhury, A., Raihan, S.Z., Muhit, M.A., Akbar, M.A., Mowla, R., 2012. Phytochemical investigation with assessment of cytotoxicity and antibacterial activities of chloroform extract of the leaves of *Kalanchoe pinnata*. Am. J. Plant Physiol. 7, 41–46.
Bodakhe, K.S., Namdeo, K.P., Bodakhe, S.H., Pandey, D.P., 2013. A new flavonol glycoside from *Kalanchoe pinnata* leaves. Asian J. Chem. 25, 9763–9765.
Bopda, O.S.M., Longo, F., Bella, T.N., Edzah, P.M.O., Taïwe, G.S., Bilanda, D.C., Tom, E.N.L., Kamtchouing, P., Dimo, T., 2014. Antihypertensive activities of the aqueous extract of *Kalanchoe pinnata* (Crassulaceae) in high salt-loaded rats. J. Ethnopharmacol. 153, 400–407.
Bosco, F.G., Arumugam, R., 2012. Ethnobotany of irular tribes in redhills, Tamilnadu, India. Asian Pac. J. Trop. Dis. 2, S874–S877.
Boscolo, O.H., Valle, L.S., 2008. Plantas de uso medicinal em Quissamã, Rio de Janeiro, Brasil. Iheringia. Sér. Bot. 63, 263–277.
Boulogne, I., Germosén-Robineau, L., Ozier-Lafontaine, H., Fleury, M., Loranger-Merciris, G., 2011. Tramil ethnopharmacological survey in Les Saintes (Guadeloupe, French West Indies): a comparative study. J. Ethnopharmacol. 133, 1039–1050.
Braz, D.C., Oliveira, L.R.S., Viana, A.F.S.C., 2013. Atividade antiulcerogênica do extrato aquoso da *Bryophyllum pinnatum* (Lam.) Kurz. Rev. Bras. Plantas Med. 15, 86–90.
Cartaxo, S.L., Souza, M.M.A., Albuquerque, U.P., 2010. Medicinal plants with bioprospecting potential used in semi-arid northeastern Brazil. J. Ethnopharmacol. 131, 326–342.
Chassagne, F., Hul, S., Deharo, E., Bourdy, G., 2016. Natural remedies used by Bunong people in Mondulkiri province (Northeast Cambodia) with special reference to the treatment of 11 most common ailments. J. Ethnopharmacol. 191, 41–70.
Chibli, L.A., Rodrigues, K.C.M., Gasparetto, C.M., Pinto, N.C.C., Fabri, R.L., Scio, E., Alves, M.S., Del-Vechio-Vieira, G., Sousa, O.V., 2014. Anti-inflammatory effects of *Bryophyllum pinnatum* (Lam.) Oken ethanol extract in acute and chronic cutaneous inflammation. J. Ethnopharmacol. 154, 330–338.
Choudhury, J., Bora, D., Baruah, D., Borah, T., Bharali, B.K., 2014. Portrayal of folk medicinal practices among the indigenous people of north Tripura district of Tripura, India. Int. J. Res. Ayurveda Pharm. 5, 480–488.
Choudhury, P.R., Choudhury, M.D., Ningthoujam, S.S., Das, D., Nath, D., Talukdar, A.D., 2015a. Ethnomedicinal plants used by traditional healers of North Tripura district, Tripura, North East India. J. Ethnopharmacol. 166, 135–148.
Choudhury, P.R., Choudhury, M.D., Ningthoujam, S.S., Mitra, A., Nath, D., Talukdar, A.D., 2015b. Plant utilization against digestive system disorder in Southern Assam, India. J. Ethnopharmacol. 175, 192–197.
Chowdhury, A., Biswas, S.K., Das, J., Karmakar, U.K., Shill, M.C., Dutta, N., 2011. Investigation of cytotoxicity and antifungal activities of petroleum ether and aqueous extracts of leaves and stems of *Kalanchoe pinnata* L. (Crassulaceae). Asian J. Plant Sci 10, 274–277.
Coe, F.G., 2008. Rama midwifery in eastern Nicaragua. J. Ethnopharmacol. 117, 136–157.
Coelho-Ferreira, M., 2009. Medicinal knowledge and plant utilization in an Amazonian coastal community of Marudá, Pará State (Brazil). J. Ethnopharmacol. 126, 159–175.
Corrêa, M.P., 1984. Dicionário de Plantas Úteis do Brasil e das Exóticas Cultivadas. Imprensa Nacional, Rio de Janeiro.
Cos, P., Hermans, N., Bruyne, T., Apers, S., Sindambiwe, J.B., Witvrouw, M., Clercq, E., Berghe, D.V., Pieters, L., Vlietinck, A.J., 2002. Antiviral activity of Rwandan medicinal plants against human immunodeficiency virus typo-1 (HIV-1). Phytomedicine 9, 62–68.
Costa, S.S., Jossang, A., Bodo, B., 1994. Patuletin acetylrhamnosides from *Kalanchoe brasiliensis* as inhibitors of human lymphocyte proliferative activity. J. Nat. Prod. 57, 1503–1510.
Costa, S.S., Souza, M.L.M., Ibrahim, T., Melo, G.O., Almeida, A.P., Guette, C., Férézou, J., Koatz, V.L.G., 2006. Kalanchosine dimilate, an anti-inflammatory salt from *Kalanchoe brasiliensis*. J. Nat. Prod. 69, 815–818.
Costa, V.P., Mayworm, M.A.S., 2011. Plantas medicinais utilizadas pela comunidade do bairro dos Tenentes – município de Extrema, MG, Brasil. Rev. Bras. Plantas Med. 13, 282–292.
Costa, A.C.O., Fernandes, J.M., Negreiros Neto, T.S., Mendonça, J.N., Tomaz, J.C., Lopes, N.P., Soares, L.A.L., Zucolotto, S.M., 2015. Quantification of chemical marker of *Kalanchoe brasiliensis* (Crassulaceae) leaves by HPLC–DAD. J. Liq. Chromatogr. Relat. Technol. 38, 795–800.
Cryer, M., Lane, K., Greer, M., Cates, R., Burt, S., Andrus, M., Zou, J., Rogers, P., Hansen, M.D.H., Burgado, J., Panayampalli, S.S., Satheshkumar, S., Day, C.W., Smee, D.F., Johnson, F.B., 2017. Isolation and identification of compounds from *Kalanchoe pinnata* having human alpha herpesvirus and vaccinia virus antiviral activity. Pharm. Biol. 55, 1586–1591.
Cruz, E.A., Silva, S.A.G., Muzitano, M.F., Silva, P.M.R., Costa, S.S., Rossi-Bergmann, B., 2008. Immunomodulatory pretreatment with *Kalanchoe pinnata* extract and its quercitrin flavonoid effectively protects mice against fatal anaphylactic shock. Int. Immunopharmacol. 8, 1616–1621.
Cruz, E.A., Reuter, S., Martin, H., Dehzad, N., Muzitano, M.F., Costa, S.S., Rossi-Bergmann, B., Buhl, R., Stassen, M., Taube, C., 2012. *Kalanchoe pinnata* inhibits mast cell activation and prevents allergic airway disease. Phytomedicine 19, 115–121.
Darmawan, A., Megawati, Fajriah, S., 2013. 3′,4′-Dimethoxy quercetin, a flavonol compound isolated from *Kalanchoe pinnata*. J. Appl. Pharm. Sci. 3, 88–90.
Devbhuti, D., Gupta, J.K., Devbhuti, P., Bose, A., 2008. Phytochemical and acute toxicity study on *Bryophyllum calycinum* Salisb. Acta Pol. Pharm. 65, 501–504.
Dimo, T., Fotio, A.L., Nguelefack, T.B., Asongalem, E.A., Kamtchouing, P., 2006. Antiinflammatory activity of leaf extracts of *Kalanchoe crenata* Andr. Indian J. Pharmacol. 38, 115–119.
Elliott, S., Brimacombe, J., 1987. The medicinal plants of Gunung Leuser National Park, Indonesia. J. Ethnopharmacol. 19, 285–317.
Esquivel, M.Z., Zolla, C., 1986. Enfermedades dermatologicas en la medicina tradicional de México. Bol. Sanit. Panam. 101, 339–347.
Ezuruike, U.F., Prieto, J.M., 2014. The use of plants in the traditional management of diabetes in Nigeria: pharmacological and toxicological considerations. J. Ethnopharmacol. 155, 857–924.
Feitosa, C.M., Freitas, R.M., Luz, N.N.N., Bezerra, M.Z.B., Trevisan, M.T.S., 2011. Acetylcholinesterase inhibition by somes promising Brazilian medicinal plants. Braz. J. Biol. 71, 783–789.
Félix-Silva, J., Silva-Júnior, A.A., Zucolotto, S.M., Fernandes-Pedrosa, M.F., 2017. Medicinal plants for the treatment of local tissue damage induced by snake venoms: an overview from traditional use to pharmacological evidence. Evid. Based Complement. Altern. Med., http://dx.doi.org/10.1155/2017/5748256.
Fernandes, J.M., Félix-Silva, J., Cunha, L.M., Gomes, J.A.S., Siqueira, E.M.S., Gimenes, L.P., Lopes, N.P., Soares, L.A.L., Fernandes-Pedrosa, M.F., Zucolotto, S.M., 2016. Inhibitory effects of hydroethanolic leaf extracts of *Kalanchoe brasiliensis* and *Kalanchoe pinnata* (Crassulaceae) against local effects induced by *Bothrops jararaca* snake venom. PLOS ONE 11, e0168658.
Ferreira, A.C.F., Rosenthal, D., Carvalho, D.P., 2000. Thyroid peroxidase inhibition by *Kalanchoe brasiliensis* aqueous extract. Food Chem. Toxicol. 38, 417–421.
Ferreira, R.T., Coutinho, M.A.S., Malvar, D.C., Costa, E.A., Florentino, I.F., Costa, S.S., Vanderlinde, F.A., 2014. Mechanisms underlying the antinociceptive, antiedematogenic and anti-inflammatory activity of the main flavonoid from *Kalanchoe pinnata*. Evid. Based Complement. Altern. Med., http://dx.doi.org/10.1155/2014/429256.
Fondjo, F.A., Kamgang, R., Oyono, J.E., Yonkeu, J.N., 2012. Anti-dyslipidemic and antioxidant potentials of methanol extract of *Kalanchoe crenata* whole plant in streptozotocin-induced diabetic nephropathy in rats. Trop. J. Pharm. Res. 11, 767–775.
Fonseca, A.G., (Master dissertation) 2014. Avaliação toxicológica aguda e subcrônica das folhas de *Kalanchoe brasiliensis* (Crassulaceae) em camundongos Swiss. Universidade Federal do Rio Grande do Norte, Natal, pp. 75.
Fonseca, F.V., Melo, M.M., Silva, J., Pereira, G.P., Dantas-Barros, A.M., 2004. Extratos de *Curcuma longa* L. e *Kalanchoe brasiliensis* Camb. no tratamento local do envenenamento por Bothrops alternatus. Rev. Bras. Farmacogn. 14, 26–29.
Fonseca, A.G., Dantas, L.S.F.R., Fernandes, J.M., Zucolotto, S.M., Lima, A.A.N., Soares, L.A.L., Rocha, H.A.O., Lemos, T.M.A.M., 2018. *In vivo* and *in vitro* toxicity evaluation of hydroethanolic extract of *Kalanchoe brasiliensis* (Crassulaceae) leaves. J. Toxicol., http://dx.doi.org/10.1155/2018/6849765.
Fonseca-Kruel, V.S., Peixoto, A.L., 2004. Etnobotânica na reserve extrativista marinha de Arraial do Cabo, RJ, Brasil. Acta Bot. Bras. 18, 177–190.
Frausin, G., Hidalgo, A.F., Lima, R.B.S., Kinupp, V.F., Ming, L.C., Pohlit, A.M., Milliken, W., 2015. An ethnobotanical study of anti-malarial plants among indigenous people on the upper Negro River in the Brazilian Amazon. J. Ethnopharmacol. 174, 238–252.
Fürer, K., Raith, M., Brenneisen, R., Mennet, M., Simões-Wüst, A.P., von Mandach, U., Hamburger, M., Potterat, O., 2013. Two new flavonol glycosides and a metabolite profile of *Bryophyllum pinnatum*, a phytotherapeutic use in obstetrics and gynaecology. Planta Med. 79, 1565–1571.
Fürer, K., Eberli, D., Betschart, C., Brenneisen, R., De Mieri, M., Hamburger, M., Mennet-von Eiff, M., Potterat, O., Schnelle, M., Simões-Wüst, A.P., von Mandach, U., 2015. Inhibition of porcine detrusor contractility by the flavonoid fraction of *Bryophyllum pinnatum* – a potential phytotherapeutic drug for the treatment of the overactive bladder syndrome. Phytomedicine 22, 158–164.

Gaind, K.N., Gupta, R.L., 1972. Alkanes, aklanols, triterpenes and sterols of *Kalanchoe pinnata*. Phytochemistry 11, 1500–1502.
Gaind, K.N., Singla, K.A., Wallace, J.W., 1981. Flavonoid glycosides of *Kalanchoe spathulata*. Phytochemistry 20, 530–531.
Garcia, D., Domingues, M.V., Rodrigues, E., 2010. Ethnopharmacological survey among migrants living in the Southeast Atlantic Forest of Diadema, São Paulo, Brazil. J. Ethnobiol. Ethnomed. 6, 1–19.
Gbolade, A., 2012. Ethnobotanical study of plants used in treating hypertension in Edo State of Nigeria. J. Ethnopharmacol. 144, 1–10.
Gehrig, H., GauBmann, O., Marx, H., Schwarzott, D., Kluge, M., 2001. Molecular phylogeny of the genus *Kalanchoe* (Crassulaceae) inferred from nucleotide sequences of the ITS-1 and ITS-2 regions. Plant Sci. 160, 827–835.
Ghasi, S., Egwuibe, C., Achukwu, P.U., Onyeanusi, J.C., 2011. Assessment of the medical benefit in the folkloric use of *Bryophyllum pinnatum* leaf among the Igbos of Nigeria for the treatment of hypertension. Afr. J. Pharm. Pharmacol. 5, 83–92.
Giovannini, P., Heinrich, M., 2009. Xki yoma' (our medicine) and xki tienda (patent medicine) – interface between traditional and modern medicine among the Mazatecs of Oaxaca, Mexico. J. Ethnopharmacol. 121, 383–399.
Gomes, D.C.O., Muzitano, M.F., Costa, S.S., Rossi-Bergmann, B., 2009. Effectiveness of the immunomodulatory extract of *Kalanchoe pinnata* against murine visceral leishmaniasis. Parasitology 137, 613–618.
Gonçalves, A.R., Wiest, J.M., Roehe, P.M., Carvalho, H.H., 2009. Citotoxicidade de plantas com indicative etnográfico para a desinfecção de água. Rev. Bras. Plantas Med. 11, 305–309.
Gupta, R., Lohani, M., Arora, S., Rehni, A.K., Chauhan, R., 2009. Anti-inflammatory activity of extracts and isolated alkaloidal fraction from leaves of *Bryophyllum pinnatum*. Pharmacologyonline 2, 873–886.
Gupta, S., Adak, S., Rajak, R.C., Banerjee, R., 2015. In-vitro efficacy of *Bryophyllum pinnatum* leaf extracts as potent therapeutics. Prep. Biochem. Biotechnol. 46, 489–494.
Gutiérrez, J.M., Warrell, D.A., Williams, D.J., Jensen, S., Brown, N., Calvete, J.J., Harisson, R.A., 2013. The need for full integration of snakebite envenoming within a global strategy to combat the neglected tropical diseases: the way forward. PLoS Negl. Trop. Dis. 7, e2162.
Gwehenberger, B., Rist, L., Huch, R., von Mandach, U., 2004. Effect of *Bryophyllum pinnatum* versus fenoterol on uterine contractility. Eur. J. Obstet. Gynecol. Reprod. Biol. 113, 164–171.
Hara, K., Someya, T., Sano, K., Sagane, Y., Watanabe, T., Wijesekara, R.G.S., 2018. Antioxidant activities of traditional plants in Sri Lanka by DPPH free radical-scavenging assay. Data Brief 17, 870–875.
Harlalka, G.V., Patil, C.R., Patil, M.R., 2007. Protective effect of *Kalanchoe pinnata* Pers (Crassulaceae) on gentamicin-induced nephrotoxicity in rats. Indian J. Pharmacol. 39, 201–205.
Herrera, A., 2008. Crassulacean acid metabolism and fitness under water deficit stress: if not for carbon gain, what is facultative CAM good for? Ann. Bot 103, 645–653.
Hossan, M.S., Hanif, A., Khan, M., Bari, S., Jahan, R., Rahmatullah, M., 2009. Ethnobotanical survey of the Tripura tribe of Bangladesh. Am. Eurasian J. Sustain. Agric. 3, 253–261.
Hubert, D.J., Céline N., Michel, N., Gogulamudi, V.R., Florence, N.T., Johnson, B.N., Bonaventure, N.T., Singh, I.P., Sehgal, R., 2013. *In vitro* leishmanicidal activity of some Cameroonian medicinal plants. Exp. Parasitol. 134, 304–308.
Hyakutake, S., Grotta, A.S., 1972. Contribuição para o estudo morfológico e anatômico de *Kalanchoe brasiliensis* Cambressèdes – Crassulaceae. Rev. Farm. Bioquim. Univ. São Paulo 10, 217–237.
Ibrahim, T., Cunha, J.M.T., Madi, K., Fonseca, L.M.B., Costa, S.S., Koatz, V.L.G., 2002. Immunomodulatory and anti-inflammatory effects of *Kalanchoe brasiliensis*. Int. Immunopharmacol. 2, 875–883.
Inta, A., Shengji, P., Balslev, H., Wangpakapattanawong, P., Trosonthi, C., 2008. A comparative study on medicinal plants used in Akha's traditional medicine in China and Thailand, cultural coherence or ecological divergence? J. Ethnopharmacol. 116, 508–517.
Islam, M.K., Saha, S., Mahmud, I., Mohamad, K., Awang, K., Uddin, S.J., Rahman, M.M., Shilpi, J.A., 2014. An ethnobotanical study of medicinal plants used by tribal and native people of Madhupur forest area, Bangladesh. J. Ethnopharmacol. 151, 921–930.
Jain, V.C., Patel, N.M., Shah, D.P., Patel, P.K., Joshi, B.H., 2010. Antioxidant and antimicrobial activities of *Bryophyllum calycinum* Salisb leaf. Pharmacologyonline 1, 393–405.
Jessica, L.K., 2008. Investigation of Kalanchoe homeobox 1 (Kh1) gene in Apical Meristems of Kalanchoe pinnatum. In: Undergraduate Honors Theses. Butler University, Indiana USA.
Joseph, B., Sridhar, S., Sankarganesh, J., Edwin, B.T., 2011. Rare medicinal plant – *Kalanchoe pinnata*. Res. J. Microbiol. 6, 322–327.
Joshi, A., Chauhan, R.S., 2013. Phytochemical analysis and cytotoxicity studies of *Bryophyllum calycinum* in BHK-21 cells A. Sch. Acad. J. Pharm. 2, 190–194.
Kadir, M.F., Sayeed, M.S.B., Mia, M.M.K., 2013. Ethnopharmacological survey of medicinal plants used by traditional healers in Bangladesh for gastrointestinal disorders. J. Ethnopharmacol. 147, 148–156.
Kadir, M.F., Sayeed, M.S.B., Setu, N.I., Mostafa, A., Mia, M.M.K., 2014. Ethnopharmacological survey of medicinal plants used by traditional health practitioners in Tanchi, Bandarban Hill Tracts, Bangladesh. J. Ethnopharmacol. 155, 495–508.
Kaewpiboon, C., Lirdprapamongkol, K., Srisomsap, C., Winayanuwattikun, P., Yongvanich, T., Puwaprisirisan, P., Svasti, J., Assavalapsakul, W., 2012. Studies of the *in vitro* cytotoxic, antioxidant, lipase inhibitory and antimicrobial activities of selected Thai medicinal plants. BMC Complement. Altern. Med., http://dx.doi.org/10.1186/1472-6882-12-217.
Kamboj, A., Saluja, A.K., 2009. *Bryophyllum pinnatum* (Lam.) Kurz.: phytochemical and pharmacological profile: a review. Pharmacog. Rev. 3, 364–374.
Kamboj, A., Saluja, A.K., 2017. Development of validated HPTLC method for quantification of stigmasterol from leaf and stem of *Bryophyllum pinnatum*. Arab. J. Chem. 10 (Suppl. 2), S2644–S2650.
Kamgang, R., Mboumi, R.Y., Fondjo, A.F., Tagne, M.A.F., N'dillé, G.P.R.M., Yonkeu, J.N., 2008. Antihyperglycaemic potential of the water–ethanol extract of *Kalanchoe crenata* (Crassulaceae). J. Nat. Med. 62, 34–40.
Khan, M., Patil, P.A., Shobha, J.C., 2004. Influence of *Bryophyllum pinnatum* (Lam.) leaf extract on wound healing in albino rats. J. Nat. Remedies 4, 41–46.
Kosalge, S.B., Fursule, R.A., 2009. Investigation of ethnomedicinal claims of some plants used by tribals of Satpuda Hills in India. J. Ethnopharmacol. 121, 456–461.
Lans, C.A., 2006. Ethnomedicines used in Trinidad and Tobago for urinary problems and diabetes mellitus. J. Ethnobiol. Ethnomed. 2, 1–11.
Lebedeva, A.A., Zakharchenko, N.S., Trubnikova, V., Medvedeva, O.A., Kuznetsova, T.V., Masgutova, G.A., Zylkova, M.V., Buryanov, Y.I., Belous, A.S., 2017. Bactericide immunomodulating, and wound healing properties of transgenic *Kalanchoe pinnata* synergize with antimicrobial peptide cecropin P1 *in vivo*. J. Immunol. Res., http://dx.doi.org/10.1155/2017/4645701.
Leitão, F., Fonseca-Kruel, V.S., Silva, I.M., Reinert, F., 2009. Urban ethnobotany in Petrópolis and Nova Friburgo (Rio de Janeiro, Brazil). Rev. Bras. Farmacogn. 19, 333–342.
Lisboa, M.S., Ferreira, S.M., Silva, M.S., 2006. Uso de plantas medicinais para tartar úlceras e gastritis pela comunidade do povoado Vila Capim, Município de Arapiraca-Al, Nordeste do Brasil. Setientibus Sér. Ciênc. Biol. (Etnobiol.) 6, 13–20.
Liu, K.C.S., Shi-Lin, Y., Roberts, M.F., Phillipson, J.D., 1989. Flavonols glycosides with acetyl substitution from *Kalanchoe gracilis*. Phytochemistry 28, 2813–2818.
Long, C., Li, R., 2004. Ethnobotanical studies on medicinal plants used by the Red-headed Yao People in Jinping, Yunnan Province, China. J. Ethnopharmacol. 90, 389–395.
Longuefosse, J., Nossin, E., 1996. Medical ethnobotany survey in Martinique. J. Ethnopharmacol. 53, 117–142.
Lorenzi, H., Matos, F.J.A., 2000. Plantas medicinais no Brasil: nativas e exóticas. Instituto Plantarum, Nova Odessa.
Machado, M.C.F.P., Melo-Júnior, M.R., 2009. Avaliação do efeito antitumoral da *Kalanchoe brasiliensis* sobre o sarcoma 180 em camundongos. Rev. Eletr. Farm. 6, 1–6.
Mahata, S., Maru, S., Shukla, S., Pandey, A., Mugesh, G., Das, B.C., Bharti, A.C., 2012. Anticancer property of *Bryophyllum pinnata* (Lam.) Oken. Leaf on human cervical cancer cells. BMC Complement. Altern. Med., http://dx.doi.org/10.1186/1472-6882-12-15.
Mahmood, A., Mahmood, A., Malik, R.N., Shinwari, Z.K., 2013. Indigenous knowledge of medicinal plants from Gujranwala district, Pakistan. J. Ethnopharmacol. 148, 714–723.
Majaz, Q., Khurshid, M., Nazim, S., Rahil, K., Siraj, S., 2011. Evaluation of antioxidant activity of *Kalanchoe pinnata* roots. Int. J. Res. Ayurveda Pharm. 2, 1772–1775.
Mabeku, L.B.K., Bille, B.E., Tchouangueu, T.F., Nguepi, E., Leundji, H., 2017. Treatment of *Helicobacter pylori* infected mice with *Bryophyllum pinnatum*, a medicinal plant with antioxidant and antimicrobial properties, reduces bacterial load. Pharm. Biol. 55, 603–610.
Maksyutina, N.P., Zub, M.R., 1969. A flavonoid bioside from the cell sap of *Kalanchoe pinnata*. Khim. Prir. Soednin. 5, 597.
Mans, D.R.A., Toelsie, J.R., Oedairadjsingh, K., Magali, I., Soekhoe, R., Bipat, R., 2015. Evaluation of Surinamese medicinal plants for their potential bronchospasmolytic effects in isolated guinea pig tracheal chains. Red. J. Med. Plant 9, 14–23.
Mathew, P.J., Unnithan, C.M., 1992. Search for Plants Having Anti-Cancer Properties Used by the Tribals of Wayanad, Malappuram and Palakkad Districts of Kerala, India. Aryavaidyan 6, 61–67.
Matthew, S., Singh, D., Jaiswal, S., Kumar, M., Jayakar, B., Bhowmik, D., 2013a. Antidiabetic activity of *Kalanchoe pinnata* (Lam.) Pers inalloxan induced diabetic rats. J. Chem. Pharm. Sci. 6, 1–7.
Matthew, S., Jain, A.K., Matthew, C., Kumar, M., Bhowmik, D., 2013b. Antidepressant activity of ethanolic extract of plant *Kalanchoe pinnata* (Lam.) Pers in mice. Indian J. Res. Pharm. Biotechnol. 1, 153–155.
Medeiros, M.F.T., Fonseca, V.S., Andreata, R.H.P., 2004. Plantas medicinais e seus usos pelos sitiantes da Reserva Rio das Pedras, Mangaratiba, RJ, Brasil. Acta Bot. Bras. 18, 391–399.
Mello, J.F., 1980. Plants in traditional medicine in Brazil. J. Ethnopharmacol. 2, 49–55.
Menon, N., Sparks, J., Omoruyi, F., 2015. Hypoglycemic and hypocholesterolemic activities of the aqueous preparation of *Kalanchoe pinnata* leaves in streptozotocin-induced diabetic rats. Asian Pac. J. Trop. Biomed. 5, 3–9.
Menon, N., Sparks, J., Omoruyi, F.O., 2016. Oxidative stress parameters and erythrocyte membrane adenosine triphosphatase activities in streptozotocin-induced diabetic rats administered aqueous preparation of *Kalanchoe pinnata* leaves. Pharmacogn. Res. 8, 85–88.
Mootoosamy, A., Mahomoodally, M.F., 2014. Ethnomedicinal application of native remedies used against diabetes and related complications in Mauritius. J. Ethnopharmacol. 151, 413–444.
Morais, S.M., Dantas, J.D.P., Silva, A.R.A., Magalhães, E.F., 2005. Plantas medicinais usadas pelos índios Tapebas do Ceará. Rev. Bras. Farmacogn. 15, 169–177.
Mora-Pérez, A., Hernández-Medel, M.R., 2016. Actividad anticonculsivante del extract metanólico de tallo y raíz de *Kalanchoe pinnata* Lam. en ratones: comparación con diazepam. Neurologia 31, 161–168.

Moreira, N.S., Nascimento, L.B.S., Leal-Costa, V., Tavares, E.S., 2012. Comparative anatomy of leaves of *Kalanchoe pinnata* and *K. crenata* in sun and shade conditions, as a support for their identification. Rev. Bras. Farmacogn. 22, 929–936.
Moreira, R.C.T., Costa, L.C.B., Costa, R.C.S., Rocha, E.A., 2002. Abordagem etnobotânica acerca do uso de plantas medicinais na Vila Cachoeira, Ilhéus, Bahia, Brasil. Acta Farm. Bonaer. 21, 205–211.
Morshed, A., Hossain, M.H., Shakil, S., Nahar, K., Rahman, S., Ferdausi, D., Hossain, T., Ahmad, I., Chowdhury, M.H., Rahmatullah, M., 2010. Evaluation of antinociceptive activity of two Bangladeshi medicinal plants, *Kalanchoe pinnata* (Lam.) Pers. and *Lagerstroemia speciosa* (L.) Pers. Adv. Nat. Appl. Sci. 4, 193–197.
Moura, V.M., Sousa, L.A.F., Santos, M.C., Raposo, J.D.A., Lima, A.E., Oliveira, R.B., Silva, M.N., Mourão, R.H.V., 2015. Plants used to treat snakebites in Santarém, western Pará, Brazil: an assessment of their effectiveness in inhibiting hemorrhagic activity induced by *Bothrops jararaca* venom. J. Ethnopharmacol. 161, 224–232.
Mourão, R.H.V., Santos, F.O., Franzotti, E.M., Moreno, M.P.N., Antoniolli, A.R., 1999. Antiinflammatory activity and acute toxicity (LD_{50}) of the juice of *Kalanchoe brasiliensis* (Comb.) leaves picked before and during blooming. Phytother. Res. 13, 352–354.
Muñoz, V., Sauvain, M., Bourdy, G., Callapa, J., Rojas, I., Vargas, L., Tae, A., Deharo, E., 2000. The search for natural bioactive compounds through a multidisciplinary approach in Bolivia. Part II. Antimalarial activity of some plants used by Mosetene Indians. J. Ethnopharmacol. 69, 139–155.
Muzitano, M.F., (Ph.D. thesis) 2006. Flavonóides de *Kalanchoe pinnata* (Crassulaceae): avanços na pesquisa da utilização desta espécie medicinal no tratamento da Leishmaniose cutânea. Universidade Federal do Rio de Janeiro, Rio de janeiro, pp. 199.
Muzitano, M.F., Cruz, E.A., Almeida, A.P., Silva, S.A.G., Kaiser, C.R., Guette, C., Rossi-Bergmann, B., Costa, S.S., 2006a. Quercitrin: an antileishmanial flavonoid glycoside from *Kalanchoe pinnata*. Planta Med. 72, 81–83.
Muzitano, M.F., Tinoco, L.W., Guette, C., Kaiser, C.R., Rossi-Bergmann, B., Costa, S.S., 2006b. The antileishmanial activity assessment of unusual flavonoids from *Kalanchoe pinnata*. Phytochemistry 67, 2071–2077.
Muzitano, M.F., Falcão, C.A.B., Cruz, E.A., Bergonzi, M.C., Bilia, A.R., Vincieri, F.F., Rossi-Bergmann, B., Costa, S.S., 2009. Oral metabolism and efficacy of *Kalanchoe pinnata* flavonoids in a murine model of cutaneous leishmaniasis. Planta Med. 75, 307–311.
Nascimento, L.B.S., Leal-Costa, M.V., Coutinho, M.A.S., Moreira, N.S., Lage, C.L.S., Barbi, N.S., Costa, S.S., Tavares, E.S., 2015. Increased antioxidant activity and changes in phenolic profile of *Kalanchoe pinnata* (Lamarck) Persoon (Crassulaceae) specimens grown under supplemental blue light. J. Photochem. Photobiol. B 89, 391–399.
Nascimento, L.B.S., Aguiar, P.F., Leal-Costa, M.V., Coutinho, M.A., Borsodi, M.P.G., Rossi-Bergmann, B., Tavares, E.S., Costa, S.S., 2018. Optimization of aqueous extraction from *Kalanchoe pinnata* leaves to obtain the highest content of an anti-inflammatory flavonoid using a response surface model. Phytochem. Anal. 28, 308–315.
Nassis, C.Z., Bagarollo, C.A., Monteiro, N.C., Ozores, D.P., Yamashiro, K., Freitas, A.L.P., 1995. Efeitos do suco extraído de folhas de *Bryiphylllum calycinum* Salisb (Crassulaceae) sobre o aprendizado da esquiva ativa, em ratos. Arq. Med. ABC 1, 7–9.
Nassis, C.Z., Salaroli, G.R., Rosa, R.C.I., Marques, F.F., Fattrah, S.A., 1996. Efeito do suco extraído das folhas de *Bryophyllum calycinum* Salisb (Crassulaceae) sobre a liberação de gonadotrofinas. Arq. Med. ABC 1, 6–10.
Nayak, B.S., Marshall, J.R., Isitor, G., 2010. Wound healing potential of ethanolic extract of *Kalanchoe pinnata* Lam. leaf – a preliminary study. Indian J. Exp. Biol. 48, 572–576.
Ngezahayo, J., Havyarimana, F., Hari, L., Stévigny, C., Duez, P., 2015. Medicinal plants used by Burundian traditional healers for the treatment of microbial diseases. J. Ethnopharmacol. 173, 338–351.
Nguelefack, T.B., Nana, P., Atsamo, A.D., Dimo, T., Watcho, P., Dongmo, A.B., Tapondjou, L.A., Njamen, D., Wansi, S.L., Kamanyi, A., 2006. Analgesic and anticonvulsant effects of extracts from the leaves of *Kalanchoe crenata* (Andrews) Haworth (Crassulaceae). J. Ethnopharmacol. 106, 70–75.
Nguelefack, T.B., Dimo, T., Dongmo, A.B., Sontia, B., Fotio, A.L., Watcho, P., Kamanyi, A., Vierling, W., 2008. Cardiovascular effects of the *n*-butanol extract from *Kalanchoe crenata* leaves. Pharm. Biol. 46, 1–8.
Nunkoo, D.H., Mahomoodally, M.F., 2012. Ethnopharmacological survey of native remedies commonly used against infectious diseases in the tropical island of Mauritius. J. Ethnopharmacol. 143, 548–564.
Nwadinigwe, A.O., 2011. Antimicrobial activities of methanol and aqueous extracts of the stem of *Bryophyllum pinnatum* Kurz (Crassulaceae). Afr. J. Biotechnol. 10, 16342–16346.
Obaseiki-Ebor, E.E., Odukoya, K., Telikepalli, H., Mitscher, L.A., Shankel, D.M., 1993. Antimutagenic activity of extracts of leaves of four common edible vegetable plants in Nigeria (West Africa). Mutat. Res. 302, 109–117.
Ogbonnia, S.O., Odimegwu, J.I., Enwuru, V.N., 2008. Evaluation of hypoglycaemic and hypolipidaemic effects of aqueous ethanolic extracts of *Treculia africana* Decne and *Bryophyllum pinnatum* Lam. and their mixture on streptozotocin (STZ)-induced diabetic rats. Afr. J. Biotechnol. 7, 2535–2539.
Ojewole, J.A.O., 2005. Antinociceptive, anti-inflammatory and antidiabetic effects of *Bryophyllum pinnatum* (Crassulaceae) leaf aqueous extract. J. Ethnopharmacol. 99, 13–19.
Okwu, D.E., Jsiah, C., 2006. Evaluation of the chemical composition of two Nigerian medicinal plants. Afr. J. Biotechnol. 5, 357–361.
Okwu, D.E., Nnamdi, F.U., 2011a. A novel antimicrobial phenanthrene alkaloid from *Bryophyllum pinnatum*. E-J. Chem. 8, 1456–1461.
Okwu, D.E., Nnamdi, F.U., 2011b. Two novel flavonoids from *Bryophyllum pinnatum* and their antimicrobial activity. J. Chem. Pharm. Res. 3, 1–10.
Ong, H.C., Nordiana, M., 1999. Malay ethno-medico botany in Machang, Kelantan, Malaysia. Fitoterapia 70, 502–513.
Osmond, C.B., 1978. Crassulacean acid metabolism: a curiosity in context. Ann. Rev. Plant Physiol. 29, 379–414.
Oufir, M., Seiler, C., Gerodetti, M., Gerber, J., Fürer, K., Eiff, M.M., Elsas, S., Brenneisen, R., von Mandach, U., Hamburger, M., Potterat, O., 2015. Quantification of bufadienolides in *Bryophyllum pinnatum* leaves and manufactured products by UHPLC–ESIMS/MS. Planta Med. 81, 1190–1197.
Ozolua, R.I., Eboka, C.J., Duru, C.N., Uwaya, D.O., 2010a. Effects of aqueous leaf extract of *Bryophyllum pinnatum* on guinea pig tracheal ring contractility. Niger. J. Physiol. Sci. 25, 149–157.
Ozolua, R.I., Idogun, S.R., Tafamel, G.E., 2010b. Acute and sub-acute toxicological assessment of aqueous leaf extract of *Bryophyllum pinnatum* (Lam.) in Sprague-Dawley rats. Am. J. Pharmacol. Toxicol. 5, 145–151.
Paiva, C.L., Batitucci, M.C.P., 2008. Avaliação do potencial efeito mutagênico do extrato bruto hidroalcoólico de *Kalanchoe brasiliensis* utilizando o teste do micronúcleo em medula óssea de roedores. In: 54° Congresso Brasileiro de Genética, Salvador, Brasil.
Paiva, L.S., Hayashi, E.A., Melo, G.O., Costa, S.S., Koatz, V.L.G., Nobrega, A., 2008. Inhibition of B cell development by kalanchosine dimalate. Int. Immunopharmacol. 8, 828–835.
Pal, S., Chaudhuri, A.K.N., 1991. Studies on the anti-ulcer activity of a *Bryophyllum pinnatum* leaf extract in experimental animals. J. Ethnopharmacol. 33, 97–102.
Panyaphu, K., On, T.V., Sirisa-ard, P., Srisa-nga, P., Chansakaow, S., Nathakarnkitkul, S., 2011. Medicinal plants of the Mien (Yao) in Northern Thailand and their potential value in the primary healthcare of postpartum women. J. Ethnopharmacol. 135, 226–237.
Pereira, R.C., Oliveira, M.T.R., Lemos, G.C.S., 2005. Plantas utilizadas como medicinais no município de Campos de Goytacazes – RJ. Rev. Bras. Farmacogn. 14, 37–40.
Perry, L.M., Metzger, J., 1980. Medicinal plants of East Asia attributed properties and uses. MIT Press, Cambridge, pp. 109–110.
Phatak, R.S., Hendre, A.S., 2015a. Free radical scavenging activities of different fractions of *Kalanchoe pinnata*. Int. J. Pharm. Tech. Res. 8, 854–863.
Phatak, R.S., Hendre, A.S., 2015b. *In vitro* antiurolithiatic activity of *Kalanchoe pinnata* extract. Int. J. Pharmacogn. Phytochem. Res. 7, 275–279.
Picking, D., Delgoda, R., Younger, N., Germosén-Robineau, L., Boulogne, I., Mitchell, S., 2015. Tramil ethnomedicinal survey in Jamaica. J. Ethnopharmacol. 169, 314–327.
Prabu, M., Kumuthakalavalli, R., 2012. Folk remedies of medicinal plants for snake bites, scorpion stings and dog bites in Eastern Ghats of Kolli Hills, Tamil Nadu, India. Int. J. Res. Ayurveda Pharm. 3, 696–700.
Rahmatullah, M., Rahman, A., Hossan, S., Taufiq-Ur-Rahman, M., Jahan, R., Mollik, A.H., 2010. A pharmacological and phytochemical evaluation of medicinal plants used by the Harbang Clan of the Tripura tribal community of Mirsharai area, Chittagong district, Bangladesh. J. Altern. Complem. Med. 16, 769–785.
Rodrigues, E., Tabach, R., Galduróz, J.C.F., Negri, G., 2008. Plants with possible anxiolytic and/or hypnotic effects indicated by three Brazilian cultures – Indians Afro-Brazilians and River-Dwellers. Stud. Nat. Prod. Chem. 35, 549–595.
Ruysschaert, S., van Andel, T., Putte, K.V., Damme, P.V., 2009. Bathe the baby to make it strong and healthy: plant use and child care among Saramaccan Maroons in Suriname. J. Ethnopharmacol. 121, 148–170.
Saikia, A.P., Ryakala, V.K., Sharma, P., Goswami, P., Bora, U., 2006. Ethnobotany of medicinal plants used by Assamese people for various skin ailments and cosmetics. J. Ethnopharmacol. 106, 149–157.
Salami, E.O., Ozolua, R.I., Okpo, S.O., Eze, G.I., Uwaya, D.O., 2013. Studies on the anti-asthmatic and antitussive properties of aqueous leaf extract of *Bryophyllum pinnatum* in rodent species. Asian Pac. J. Trop. Med. 6, 421–425.
Sandberg, F., Cronlund, A., 1982. An ethnopharmacological inventory of medicinal and toxic plants from Equatorial Africa. J. Ethnopharmacol. 5, 187–204.
Sanz-Biset, J., Campos-de-la-Cruz, J., Epiquién-Rivera, M.A., Cañigueral, S., 2009. A first survey on the medicinal plants of the Chazuta valley (Peruvian Amazon). J. Ethnopharmacol. 122, 333–362.
Sarkhel, S., 2014. Ethnobotanical survey of folklore plants used in treatment of snakebite in Paschim Medinipur district, West Bengal. Asian Pac. J. Trop. Biomed. 4, 416–420.
Schiavo, P.A., (M.Sc. thesis) 2005. Atividade antiviral de *Kalanchoe brasiliensis* ("saião") frente a herpesvírus tipo I *in vitro*. Universidade Federal do Rio de Janeiro, Rio de Janeiro, pp. 111.
Schuler, V., Suter, K., Fürer, K., Eberli, D., Horst, M., Betschart, C., Brenneisen, R., Hamburger, M., Mennet, M., Schnelle, M., Simões-Wüst, A.P., von Mandach, U., 2012. *Bryophyllum pinnatum* inhibits detrusor contractility in porcine bladder strips – a pharmacological study towards a new treatment option of overactive bladder. Phytomedicine 19, 947–951.
Sebastian, M.K., Bhandari, M.M., 1984. Medico-ethno botany of Mount Abu, Rajasthan, India. J. Ethnopharmacol. 12, 223–230.
Sharif, A., Akhtarl, M.F., Akhtar, B., Saleem, A., Manan, M., Shabbirl, M., Ashaf, M., Peerzada, S., Ahmed, S., Raza, M., 2017. Genotoxic and cytotoxic potential of whole plant extracts of *Kalanchoe laciniata* by Ames and MTT assay. EXCLI J. 16, 593–601.
Sharker, S.M., Hossain, M.K., Haque, M.R., Chowdhury, A.A., Kaisar, M.A., Hasan, C.M., Rashid, M.A., 2012. Chemical and biological studies of *Kalanchoe pinnata* (Lam.) growing in Bangladesh. Asian Pac. J. Trop. Biomed., S1317–S1322.

Sharma, A., Bhot, M., Chandra, N., 2014. *In vitro* antibacterial and antioxidant activity of *Bryophyllum pinnatum* (Lam.) Kurz. Int. J. Pharm. Pharm. Sci. 6, 558–560.

Sharma, A.L., Bhot, M.A., Chandra, N., 2014a. Gastroprotective effect of aqueous extract and mucilage from *Bryophyllum pinnatum* (Lam.) Kurz. Anc. Scice Life 33, 252–258.

Siddiqui, S., Faizi, S., Siddiqui, B.S., Sultana, N., 1989. Triterpenoids and phenanthrenes from leaves of *Bryophyllum pinnatum*. Phytochemistry 28, 2433–2438.

Sikdar, M., Dutta, U., 2008. Traditional phytotherapy among the Nath people of Assam. Ethno-Medicine 2, 39–45.

Silva, S.A.G., Costa, S.S., Mendonça, S.C.F., Silva, E.M., Moraes, V.L.G., Rossi-Bergmann, B., 1995. Therapeutic effect of oral *Kalanchoe pinnata* leaf extract in murine leishmaniasis. Acta Trop. 60, 201–210.

Silva, M.G., Diniz, M.F.F.M., Oliveira, R.A.G., 2002. Fitoterápicos: Guia do Profissional de Saúde. Ed. Universitária, João Pessoa.

Silva, M.S., Antoniolli, A.R., Batista, J.S., Mota, C.N., 2006. Plantas medicinais usadas nos distúrbios do trato gastrintestinal no povoado Colônia Treze, Lagarto, SE, Brasil, 20. Acta Bot. Bras., pp. 815–829.

Silva, J.G., (M.Sc. thesis), 2007. Avaliação do potencial farmacológico de *Kalanchoe brasiliensis* Cambess. Universidade Federal de Pernambuco, Recife, pp. 88.

Silva, J.G., Pereira, M.S.V., Gurgel, A.P.D., Siqueira-Júnior, J.P., Souza, I.A., 2009. Atividade inibitória das folhas e caule de *Kalanchoe brasiliensis* Cambess frente a microrganismos com diferentes perfis de resistência a antibióticos. Rev. Bras. Farmacogn. 19, 790–794.

Simões-Wüst, A.P., Grãos, M., Duarte, C.B., Brenneisen, R., Hamburger, M., Mennet, M., Ramos, M.H., Schnelle, M., Wächter, R., Worel, A.M., von Mandach, U., 2010. Juice of *Bryophyllum pinnatum* (Lam.) inhibits oxytocin-induced increase of the intracellular calcium concentration in human myometrial cells. Phytomedicine 17, 980–986.

Singh, N., Kaushik, N.K., Mohanakrishnan, D., Tiwari, S.K., Sahal, D., 2015. Antiplasmodial activity of medicinal plants from Chhoranagpur plateau, Jharkhand, India. J. Ethnopharmacol. 165, 152–162.

Sowemimo, A.A., Fakoya, F.A., Awopetu, I., Omobuwajo, O.R., Adesanya, S.A., 2007. Toxicity and mutagenic activity of some selected Nigerian plants. J. Ethnopharmacol. 113, 427–432.

Sreekeesoon, D.P., Mahomoodally, M.F., 2014. Ethnopharmacological analysis of medicinal plants and animals used in the treatment and management of pain in Mauritius. J. Ethnopharmacol. 157, 181–200.

Srithi, K., Trisonthi, C., Wangpakapattanawong, P., Balslev, H., 2012. Medicinal plants used in Hmong women's healthcare in northern Thailand. J. Ethnopharmacol. 139, 119–135.

Stobart, A.K., McLaren, I., Thomas, D.R., 1967. Chlorophylls and carotenoids of colourless callus, green callus and leaves of *Kalanchoe crenata*. Phytochemistry 6, 1467–1474.

Supratman, U., Fujita, T., Akiyama, K., Hayashi, H., 2000. New insecticidal bufadienolide, bryophyllin C, from *Kalanchoe pinnata*. Biosci. Biotechnol. Biochem. 64, 1310–1312.

Supratman, U., Fujita, T., Akiyama, K., Hayashi, H., Murakami, A., Sakai, H., Koshimizu, K., Ohigashi, H., 2001. Anti-tumor promoting activity of bufadienolides from *Kalanchoe pinnata* and *K. daigremontiana* × *tubiflora*. Biosci. Biotechnol. Biochem. 65, 947–949.

Tangjang, S., Namsa, N.D., Aran, C., Litin, A., 2011. An ethnobotanical survey of medicinal plants in the Eastern Himalayan zone of Arunachal Pradesh, India. J. Ethnopharmacol. 134, 18–25.

Tarafdar, R.G., Nath, S., Talukdar, A.D., Choudhury, M.D., 2015. Antidiabetic plants used among the ethnic communities of Unakoti district of Tripura, India. J. Ethnopharmacol. 160, 219–226.

Tarak, D., Namsa, N.D., Tangjang, S., Arya, S.C., Rajbonshi, B., Samal, P.K., Mandal, M., 2011. An inventory of the ethnobotanicals used as anti-diabetic by a rural community of Dhemaji district of Assam, Northeast India. J. Ethnopharmacol. 138, 345–350.

Tariq, A., Mussarat, S., Adnan, M., 2015. Review on ethnomedicinal, phytochemical and pharmacological evidence of Himalayan anticancer plants. J. Ethnopharmacol. 164, 96–119.

Tatsimo, S.J.N., Tamokou, J.D., Havyarimana, L., Csupor, D., Forgo, P., Hohmann, J., Kuiate, J., Tane, P., 2012. Antimicrobial and antioxidant activity of kaempferol rhamnoside derivatives from *Bryophyllum pinnatum*. BMC Res. Notes 5, 1–6.

The Plant List, 2010. Version 1. Published on the Internet http://www.theplantlist.org/ (accessed February 2019).

Torres-Santos, E.C., Silva, A.G., Costa, S.S., Santos, A.P.P.T., Almeida, A.P., Rossi-Bergmann, B., 2003. Phytother. Res 17, 801–803.

Trevisan, M.T.S., Bezerra, M.Z.B., Santiago, G.M.P., Feitosa, C.M., 2006. Atividades larvicida e anticolinesterásica de plantas do gênero *Kalanchoe*. Quim. Nova 29, 415–418.

Tropicos, 2019. http://tropicos.org/Name/8900471 and http://tropicos.org/Name/8900302 (accessed February 2019).

Ufelle, S.A., Ukaejiofo, E.O., Neboh, E.E., Achukwu, P.U., Nwagha, U.I., Ghasi, S., 2011. The effect of crude methanolic leaf extract of *Bryophyllum pinnatum* on some haematological parameters in Wistar rats. Res. J. Pharmacol. 5, 14–17.

Umbuzeiro-Valent, G., Roubicek, D.A., Haebisch, E.M.A.B., 1999. Mutagenic and antimutagenic evaluation of the juice of the leaves of *Bryophyllum calycinum* (*Kalanchoe pinnata*), a plant with antihistamine activity. Environ. Mol. Mutagen. 33, 325–327.

Wächter, R., Brenneisen, R., Hamburger, M., Mennet, M., Schnelle, M., Worel, A.M., Simões-Wüst, A.P., von Mandach, U., 2011. Leaf press juice from *Bryophyllum pinnatum* (Lamarck) Oken induces myometrial relaxation. Phytomedicine 19, 74–82.

Wet, H., Nzama, V.N., van Vuuren, S.F., 2012. Medicinal plants used for the treatment of sexually transmitted infections by lay people in northern Maputaland, KwaZulu – Natal Province, South Africa. South Afr. J. Bot. 78, 12–20.

Xavier, T.F., Kannan, M., Auxilia, A., 2015. Observation on the traditional phytotherapy among the Malayali tribes in Eastern Ghats of Tamil Nadu, South India. J. Ethnopharmacol. 165, 198–214.

Xiuzhen, Y., Kuohsiung, L., Takashi, Y., 1992. Isolation and identification of cytotoxic components from *Bryophyllum pinnatum*. Chin. J. Cancer Res. 4, 1–3.

Yadav, N.P., Dixit, V.K., 2003. Hepatoprotective activity of leaves of *Kalanchoe pinnata* Pers. J. Ethnopharmacol. 86, 197–202.

Yadav, M., Gulkari, V., Wanjari, M.M., 2016. Bryophyllum pinnatum leaf extracts prevent formation of renal calculi in lithiatic rats. Anc. Sci. Life 36, 90–97.

Yasir, F., Waqar, M.A., 2011. Effect of indigenous plant extracts on calcium oxalate crystallization having a role in urolithiasis. Urol. Res. 39, 345–350.

Yemele, M.D., Telefo, P.B., Lienou, L.L., Tagne, S.R., Fodouop, C.S.P., Goka, C.S., Lemfack, M.C., Moundipa, F.P., 2015. Ethnobotanical survey of medicinal plants used for pregnant women's health conditions in Menoua division-West Cameroon. J. Ethnopharmacol. 160, 14–31.

Yemitan, O.K., Salahdeen, H.M., 2005. Neurosedative and muscle relaxant activities of aqueous extract of *Bryophyllum pinnatum*. Fitoterapia 76, 187–193.

Zakharchenko, N.S., Belous, A.S., Biryukova, Y.K., Medvedeva, O.A., Belyakova, A.V., Masgutova, G.A., Trubnikova, E.V., Buryanov, Y.I., Lebedeva, A.A., 2017. Immunomodulating and Revascularizing Activity of Kalanchoe pinnata Synergize with Fungicide Activity of Biogenic Peptide Cecropin P1. J. Immunol. Res, 1–9, ID 3940743.

Zappi, D., 2015. *Crassulaceae* in Lista de Espécies da Flora do Brasil. Jardim Botânico do Rio de Janeiro http://floradobrasil.jbrj.gov.br/jabot/floradobrasil/FB22581 (accessed January 2019).