Use of plants of the genus *kalanchoe* as a potential treatment for inflammatory diseases

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ABSTRACT
Medicinal plants have been used throughout civilizations, accumulating empirical knowledge for treatment and prevention of diseases and often incorporate plant derivatives into treatments. Plants contain a variety of chemical compounds, classified as primary and secondary metabolites. These substances have applications in the pharmaceutical industry, colorants, and flavorings due to their beneficial properties. Thus, the genus Kalanchoe has several applicabilities in ethnomedicine. The objective of the work is to show the medicinal use of the extract of plant species of the genus kalanchoe, as treatments of diseases in articles from the years 2013 to 2023. It has shown anti-inflammatory, antitumor, healing, antidiabetic, antiulcerogenic, antihypertensive, detrusor relaxant, neuroprotective, antiviral, antimicrobial, antiasthmatic, antitussive and nephroprotective action.

Keywords: *Kalanchoe*, Phytochemical compounds, Inflammation, Pathology.

1 INTRODUCTION

Medicinal plants have always been used in the daily life of civilizations, both ancient and modern, so that, over time, empirical and effective knowledge have been acquired for the relief of diseases. This practice helps the human being a lot over time in relation to the search for treatment and

also prevention (Borges *et al.*, 2020). Currently, traditional methods with herbal plants remain constant, as a large part of the population sees this habit as safe, especially in emerging countries. Physicians also use the derivatives of these plants in prescriptions (Firmo *et al.*, 2011).

Plants have a wide variety of chemical compounds, which can be grouped into primary and secondary metabolites. Primary metabolites are substances produced by all plants and play a direct role in their growth and development. In contrast, secondary metabolites have a high specificity and a crucial role in the evolution of plants along with other living organisms, e.g., protection of plants against biotic and abiotic stresses. These secondary metabolites generally fall into three main classes of molecules: terpenes, phenolic compounds, and nitrogenous. In addition, they are widely used in the biopharmaceutical and various commercial industries, due to their beneficial properties, such as the production of medicines, dyes, and flavorings (Borges; Amorim, 2020).

With industrialization, herbal medicines, processed medicines derived from medicinal plants, came to the fore, which with current technology managed to enter the market, but with the chemical synthesis of drugs and the lack of scientific proof in the efficiency of these substances, brought a drop in the use of herbal medicines (Gadelha *et al.*, 2013). However, the association of the popular history and the clinical results of the use of herbal medicines collaborates in the satisfaction of people and doctors about the efficacy of the product. And it is even more indispensable, because politically it becomes recommended in the Unified Health System (SUS), mainly reaching primary care in which it ensures symptoms in the preliminary phase of diseases, and also aims at a more sustainable system and social participation (ROSA *et al.*, 2011).

Second classification of the *Angiosperm Phylogeny Group* IV (APG IV) the genus *Kalanchoe* It has a number of 145 species. Thus, it has a complex taxonomy with numerous synonyms of species, thus establishing the integration of the genus *Bryophyllum* to gender *Kalanchoe* (Descoings, 2006)soon *Bryophyllum* It is considered a heterotypic synonym, an example of which we have the species *Calancho Creta* (Andrews) Haw, sinonímia *Kalanchoe brasiliensis* Larrañaga e *Pencho Pinnata* (Lam.) Pers., synonymy *Bryophila Kalisinama* Salisb, all exotic species in Brazil (Goebel; Caddah; Giuffrè, 2020).

The genus *Kalanchoe*, in which it is part of the Crassulaceae family and spreads to continents in tropical and subtropical zones, such as Africa, Asia and America, contributes greatly to the treatment of diseases such as gastric ulcers, ear infections, arthritis, cough, skin lesions and inflammations as well as periodontals. In ethnomedicine, the crude extract or juice points to anticancer and healing properties, as an example, in the State of Rio Grande do Norte, Brazil, the leaves of *Kalanchoe pinnata* Lam. are used in direct application to wounds in the search for healing, as well as in the treatment of gastritis and ulcers. (De Araújo *et al.*, 2019; Stefanowicz-Hajduk *et al.*, 2020)tag.

Thus, the objective of this work was to carry out a bibliographic review of the articles published between the years 2013 and 2023, which show the medicinal use of the extract of plant species of the genus *Kalanchoe*, focusing on the treatment of diseases in general, as well as the identification of these plants and secondary metabolites responsible for the biological activity against pathologies, in addition to the experimental models used to evaluate the efficiency of these active compounds.

2 MATERIAL AND METHOD

The work is defined with a literature review, and is based on the following question: Which inflammatory diseases can be treated with plant species of the genus *kalanchoe* ?

In the review search, articles were searched in the following databases: *Scopus, PubMed,* and *Scielo*, based on a pre-defined period from January 2013 to May 2023. The keywords used were "*kalanchoe and disease or pathology or treatment*". The selection of articles was carried out in June 2023, where, through the reading of the titles and abstracts of the papers, the classification was made, and in a situation of insufficiency of this measure, the article was read in full. It is noteworthy that the analysis of the articles was only possible under conditions of easy access and in English, Spanish and Portuguese.

After being classified, the articles were fully read and selected according to the criteria (Chart 1). The selected works had to present a method of treatment for any disease or pathology that used the extract or herbal medicine of some species of the genus *Kalanchoe*. Thus, the following main information was extracted from the articles: scientific name of the plant, active compound, disease, region of the plant for the extraction of the compounds, type of extract and induction of the disease.

Table 1: Selections of articles (Exclusion and Inclusion Criteria), Teresina – PI, 2023

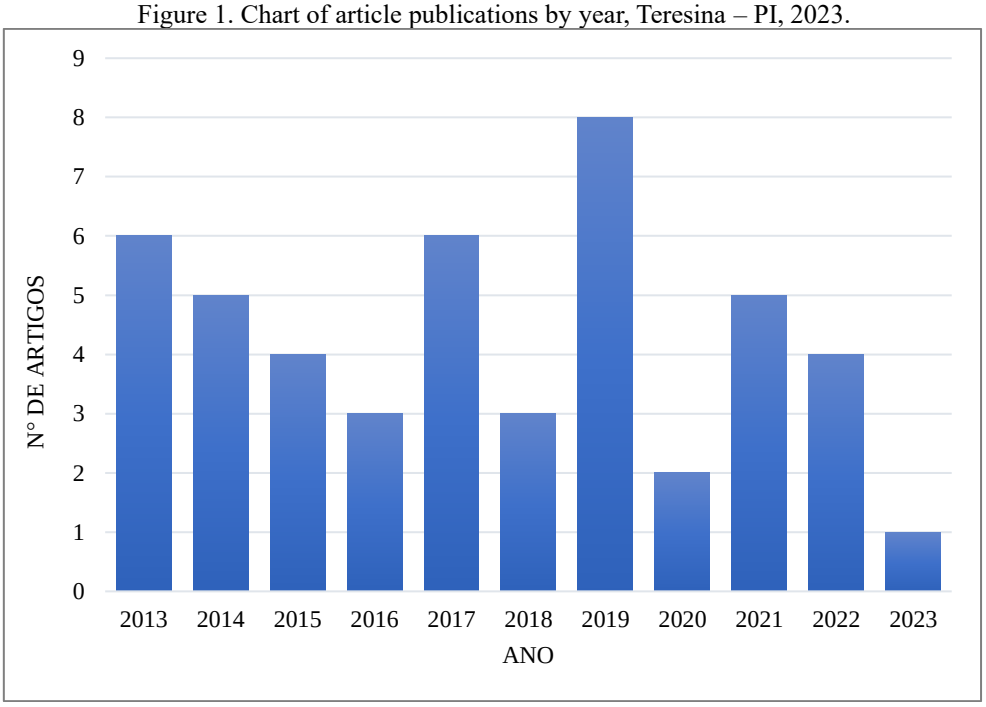
Database searches (*Scopus, PubMed and Scielo*)	
Exclusion Criteria	Inclusion criteria
- Work be a Thesis or Dissertation; - Work be a review article, patent document, congress abstract, book chapter, and editorials - Use a human clinical trial model; - The article must be written in languages other than English, Spanish and Portuguese.	- Use of herbal medicines and/or compounds isolated from the plant as a form of treatment for diseases in general; - Conducting tests in animal experiments (*in vivo*) and *in vitro*

Source: The author

3 RESULT AND DISCUSSION

Initially, the searches totaled 329 articles in the *Scopus, PubMed* and *Scielo* databases. After this stage, 283 files that were duplicates or were not aligned with the focus of this review were excluded, resulting in a total of 46 studies (Table 1), which were used for the elaboration of this article. In terms of distribution by year, it was observed that 2019 had the highest number of publications, followed by 2017 and 2013, with a total of 8, 6 and 6 articles, respectively. On the other hand, the year 2023 had a single published paper, representing the lowest number of contributions in the period analyzed (Figure 1).

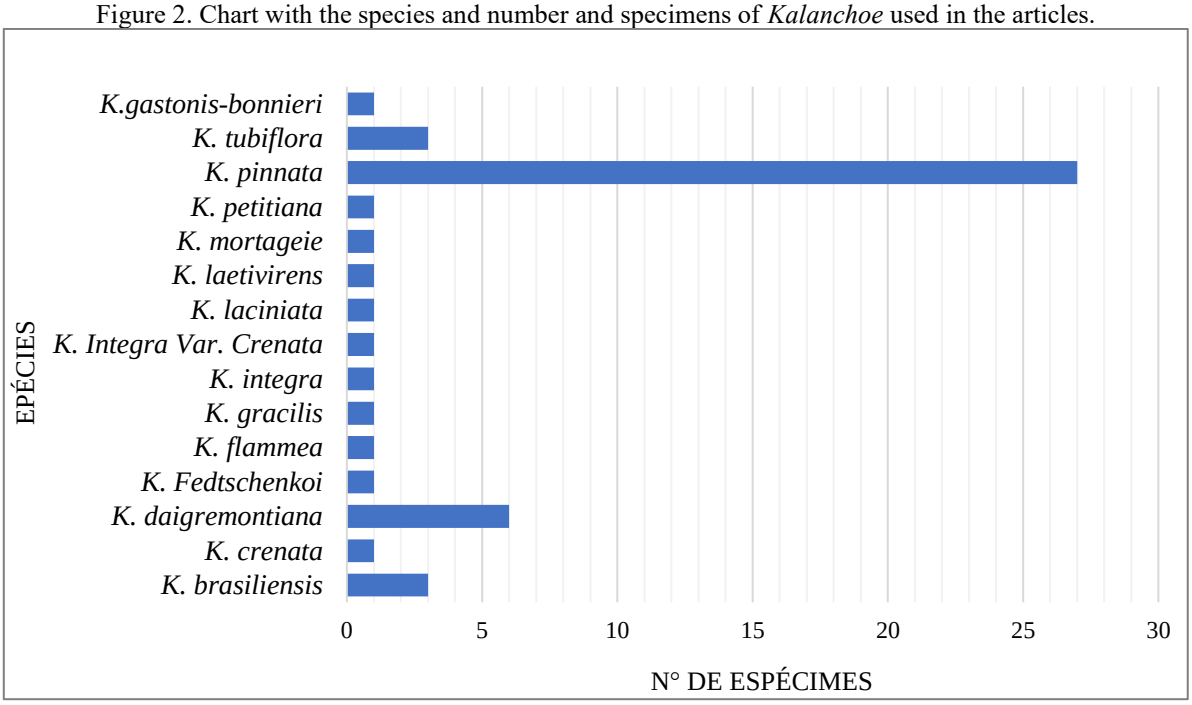
Figure 1. Chart of article publications by year, Teresina – PI, 2023.



Source: The author

According to the researched works, 14 species and a variety of *Kalanchoe*. In all, the number of specimens was totaled 50, taking into account studies that had more than one species in the research. The species with the highest number of articles was *Pencho Pinnata* (Lam.) Pers. [sin. *Bryophila pinnacle* (Lam.) Kurz] with a number of 27 articles, being the best-known representative of the genre (Bogucka-Kocka *et al.*, 2018). Figure 2 shows that the *K. pinnata* was the most abundant and followed by the *K. daigremontiana*, *K. brasiliensis*, *K. tubiflora* with 6, 3 and 3 specimens respectively. And the other species were recorded in only one article.

Figure 2. Chart with the species and number and specimens of *Kalanchoe* used in the articles.



Source: The author

There is a specific interest in some species because of their unique health properties. So a variety of plant parts are used to make various types of extracts. And among the selected works, the botanical genus had a wide applicability in several diseases, as an anti-inflammatory effect (Chibli *et al.*, 2014; De Araújo *et al.*, 2019; Ferreira *et al.*, 2014)antitumor (Arias-Gonzalez *et al.*, 2018; Hseu *et al.*, 2019; Hsieh *et al.*, 2016; Huang *et al.*, 2013; Kayuppaipoo *et al.*, 2014; Palumbo *et al.*, 2019; Stefanowicz-Hajduk *et al.*, 2020; Stefanowicz-Hajduka *et al.*, 2022)healing (Mekonnen *et al.*, 2013)antidiabetic (Agüero-Hernández *et al.*, 2020; Religion-Neverred *et al.*, 2021; Menon *et al.*, 2015; Patil *et al.*, 2013; Ramon *et al.*, 2023), antiulcerogenic (Braz; Olive tree; Viana, 2013; De Araújo *et al.*, 2018; Shaffer *et al.*, 2017), anti-hypertensives (Bopda *et al.*, 2014), detrusor relaxant (Bachmann *et al.*, 2017; Fürer *et al.*, 2015) Neuroprotective (Anadozie, S.O. *et al.*, 2019; storeman *et al.*, 2021; Kukuia *et al.*, 2015; Mora-Pérez *et al.*, 2016), antiviral (Aoki *et al.*, 2014; Cryer *et al.*, 2017; Wang *et al.*, 2013), antimicrobial (Elizondo-Luévano *et al.*, 2021; The desire to be forgotten *et al.*, 2017; Lebedeva *et al.*, 2017; Mayorga *et al.*, 2019; Richwagen *et al.*, 2019; Rivero-Pérez *et al.*, 2022; Zakharchenko *et al.*, 2017) anti-asthmatic and antitussive (Salami *et al.*, 2013) and nephroprotectant (Anadozie *et al.*- 2018 Dighade *et al.*, 2021; Hewagama *et al.*, 2022; Kamgang *et al.,* 2015; Sohgaura *et al.*, 2019).

Table 1. Description of the articles selected in the review, Teresina – PI, 2023

	Species and active compound(s)	Pathology	Starts from planta	Type of Extrato	Induction of pathology	Reference
	K. pinnata kaempferitrin e kaempferol	Type 2 diabetes	Leaves	Hydroalcoholic	Oral administration of starch – *in vivo*	(Agüero-Hernández *et al.*, 2020)
	B. pinnatum Antioxidants	Short-term memory loss	Leaves	Aqueous	Intraperitoneal injection of carbon tetrachloride – *in vivo*	(Anadozie *et al.*, 2019)
	B. pinnatum Antioxidants	Renal oxidative damage	Leaves	Aqueous	Intraperitoneal injection of carbon tetrachloride – *in vivo*	(Anadozie *et al.*, 2018)
	K. pinnata Quercetin and gallic acid	Viral infection	Leaves	Methanolic	Hepatitis C virus cell infection – *in vitro*	(Aoki *et al.*, 2014)
	K. flammea Coumaric Acid and Palmitic Acid	Prostate Cancer	Leaves	Ethyl Acetate	Human prostate cells – *in vitro*	(Arias-González *et al.*, 2018)
	K. Integra var. Crenata Flavonoids	Cardiotoxicity	Leaves	Ethanolic	Doxorubicin injection – *in vivo*	(Asiedu-Gyekye *et al.*, 2022)
	B. pinnatum Bufadienolids and flavonoid aglycones	Bexiga hiperativa	Leaves	Methanolic	K+ solution in porcine urinary bladders – *in vitro*	(Bachmann *et al.*, 2017)
	B. pinnatum Flavonoids, alkaloids, phenols, tannins and saponins	Memory loss	Bark and Leaves	Methanolic	Intraperitoneal injection of scopolamine hydrobromide – *in vivo*	(Bhandari *et al.*, 2021)
	K. pinnata Flavonoids and polyphenols	Hypertension	Leaves	Aqueous	Oral administration of NaCl solution – *in vivo*	(Bopda *et al.*, 2014)
	B. pinnatum Flavonoids and tannins	Gastric ulcer	Leaves	Aqueous	Intraperitoneal injection of indomethacin – *in vivo*	(Braz; Oliveira; Viana, 2013)
	B. pinnatum Rutin, quercetin, and luteolin	Acute and chronic skin inflammation	Leaves	Ethanolic	Topical application of Croton oil, arachidonic acid, phenol, capsaicin and ethyl phenylpropiolate – *in vivo*	(Chibli *et al.*, 2014)
	K. pinnata KPB-100 and KPB-200 (Unidentified)	Viral infection	Roots	Methanolic	Infection with human herpesvirus alfa and vaccinia virus in Vero cell culture – *in vitro*	(Cryer *et al.*, 2017)

	K. brasiliensis e K. pinnata The bow of the bow; The throne, the throne of the throne, the throne of the throne	Topical inflammation	Leaves	Aqueous	Induction of ear endema by croton oil and paw edema induced by carrageenan – *in vivo*	(De Araújo *et al.*, 2019)
	K. brasiliensis e K. pinnata The bow of the bow; the throat, the throat, the throat, the throat	Gastric lesions	Leaves	Aqueous	Oral induction with ethanol and indomethacin – *in vivo*	(De Araújo *et al.*, 2018)
	B. pinnatum Flavonoides, polifenóis e saponinas	Multifatorial urolithiase	Leaves	Aqueous	Oral administration of ethylene glycol – *in vivo*	(Dighade *et al.*, 2021)
	K. daigremontiana Quercetin	Parasitic infection	Leaves	Methanolic	Microassay with *Entamoeba histolytica* and *Trichomonas vaginalis* – *in vitro*	(Elizondo-Luévano *et al.*, 2021)
	K. pinnata Quercithin	Nausea, vomiting, pain, and inflammation	Flowers	Aqueous (ethyl acetate and butanol fractions)	Induction of abdominal contortions by subcutaneous acetic acid with saline solution or indomethacin; Subcutaneous carrageenan-induced pleurisy with saline or dexamethasone in the pleural cavity; Ear edema induced by croton oil or dexamethasone – *in vivo*	(Ferreira *et al.*, 2014)
	B. pinnatum Flavonoids	Overactive bladder syndrome	Leaves	Methanoid (fractions of flavonoids, bufadienolides and polar)	Electrical mediation by organ bath in porcine bladder detrusor muscle – *in vitro*	(Fürer *et al.*, 2015)
	K. laciniata Flavonoids, tannins and polyphenolic compounds	Urolitidasis and nephrolithiasis	Leaves	Aqueous, ethanolic and hexane	CaOx induction in synthetic urine system – *in vitro*	(Hewagama; Hewawasam, 2022)
	K. tubiflora Kalantuboside B	Cancer	Whole Plant	Ethanolic	Human melonoma cell and murine tumor – *in vitro*; subcutaneous injection into the flanks of tumor cells suspended in matrix gel – *in vivo*	(Hseu *et al.*, 2019)

	K. tubiflora (Unidentified)	Cancer	Whole Plant	Aqueous	Human lung adenocarcinoma cell line – *in vitro*; subcutaneous inoculation into the flank of lung cancer cells – *in vivo*	(Hsieh *et al.*, 2016)
K. tubiflora Cardenolideos and Glycosideos Bufadienolideos		Cancer	Whole Plant	Ethanolic (n-hexane, EtOAc and n-BuOH fractions)	Human cell linhas: pulmonary adenocarcinoma epithelial; oral adenoesquamous carcinoma; melanoma; Myelocytic leukemia – *in vitro*	(Huang *et al.*, 2013)
B. laetivirens (Unidentified)		Cancer	Leaves	Metalnolic (fractions of water and dichloromethane)	Human Lung Cancer Cell Line – *In Vitro*	(Kaewpiboon *et al.*, 2014)
K. crenata Tannins, triterpenes and polyphenols		Renal insufficiency	Whole Plant	Methanolic	Intravenous injection of adriamycin – *in vivo*	(Kamgang; Fondjo; Oyono, 2015)
K. daigremontiana Bufadienolids		Oxidation	Roots	Aqueous methanol (bufadienolide fraction)	Exposure of peroxynitrite in human blood plasma – *in vitro*	(Kołodziejczyk-Czepas *et al.*, 2016)
B. pinnatum Alcaloides, fenóis, flavonoides, taninos, antraquinonas e esteroides		Bacterial infection	Leaves	Methanolic and ethyl acetate	Oral inoculation of a Helicobacter *pylori suspension* – *in vivo*	(The desire must be *et al.*, 2017)
K. Integra (Unidentified)		Depression	Leaves	Aqueous	Treatment with reserpine, α-methyl paratyrosine (AMPT) or p-chlorophenylalanine – *in vivo*	(Kukuia *et al.*, 2015)
	K. pinnata (Wild and Transgenic) Flavonoids or lectins	Bacterial infection in wounds	Leaves	Aqueous	Modelling of purulent infection with *Staphylococcus aureus* and/or *Pseudomonas aeruginosa* – *in vivo*	(Lebedeva *et al.*, 2017)
	K. daigremontiana Ascorbic acid, phenols, gallic acid, flavonoids and quercetin	Diabetes mellitus	Leaves	Gross	Dieta *ad libitum* líquida hiperglicêmica rica em sacarose – *in vivo*	(Madariaga-Navarrete *et al.*, 2021)
	K. brasiliensis Flavonoids	Bacterial infection	Leaves	Hydroethenolic	Assay with 5 strains of *Salmonella spp.* – *in vitro*	(Mayorga *et al.*, 2019)
	K. petitiana Polyphenols, alkaloids, flavonoids and tannins	Wound healing	Leaves	Hydroalcoholic (aqueous, methanolic and chloroform fractions)	Skin excision and incision with scissors – *in vivo*	(Mekonnen *et al.*, 2013)

	K. pinnata Flavonoides, polifenóis, triterpenoides, fitoesteróis e zinco	Diabetes mellitus	Leaves	Aqueous	Single intraperitoneal injection of streptozotocin – *in vivo*	(Menon; Sparks; Omoruyi, 2015)
	K. pinnata Sterols and terperes	Convulsion	Root or Stem	Methanolic	Oral induction of pentylenetetrazole – *in vivo*	(Mora-Pérez; Hernández-Medel, 2016)
	Q. Gastonis-Bonnieri Glycositized lignans	Benign prostatic hyperplasia	Leaves, flowers and underground parts	Aqueous	Human cell culture of benign prostatic hyperplasia – *in vitro*	(Palumbo *et al.*, 2019)
	K. pinnata (Unidentified)	Diabetes mellitus	Leaves	Petroleum ether, chloroform, dichlororetomethane and aqueous fractions	Intraperitoneal injection of streptozotocin in citatro buffer – *in vivo*; Incubation of rat pancreatic lhotas in glucose – *in vitro*	(Patil *et al.*, 2013)
	K. pinnata Quercetin, kaempferol, apigenin, epigallocatechin gallate and avicularin	Diabetes Mellitus	Leaves	Dimethyl sulfoxide	Human Diabetic Muscle Myoblast Cell – *In Vitro*	(Ramon *et al.*, 2023)
	K. mortageie K . *Fedtschenkoi* Kaempferol, quercetin, phenolic compounds, caffeic acid, p-coumaric acid and ferulic acid	Bacterial infections	Leaves, flowers and stem	Aqueous and ethanolic	Assay with ESKAPE bacterial strains – *in vitro*	(Richwagen *et al.*, 2019)
	K. Daigremontiana Flavonoids, flavones, saponins, alkaloids, xanthones, polyphenols, tannins and derivatives of pyrazol-5-carboxamide	Parasite and bacterial infections	Leaves	Hydroalcoholic	Ensaio com ovos de *Haemonchus contortus*; e cepas de *Staphylococcus aureus, Bacillus subtilis, Salmonella typhimurium, Pseudomonas aeruginosa, Listeria monocytogenes* e *Escherichia coli – in vitro*	(Rivero-Pérez *et al.*, 2022)
	Bee. Hindsight Flavonoids	Asthma and coughing spells	Leaves	Aqueous	Histamine Aerosol Exposure for Asthma and Citric Acid for Cough – *In Vivo*	(Salami *et al.*, 2013)
	K. pinnata Quercetin	Peptic ulcers	Leaves	Hydroethanolic (ethyl acetate fraction)	Oral induction of gastric lesions by gavage with ethanol HCl – *in vivo*	(Sobreira *et al.*, 2017)
	K. pinnata Flavonoids and polyphenols	Nephrolithia	Leaves	Hydroethanolic	Induction of ammonium chloride and ethylene glycol administered via	(Sohgaura; Bigoniya; Shrivastava, 2019)

					drinking water – *in vivo*	
	K. daigremontiana Bufadienolids	Cancer	Leaves	Ethanolic (aqueous, dichloromethanelic, and bersaldegenin 1,3,5-orthoacetate fractions)	Human cervical adenocarcinoma, ovarian cancer, breast cancer, malignant melanoma and keratinocyte cell lines – *in vitro*	(Stefanowicz-Hajduk *et al.*, 2020)
	K. daigremontiana Bufadienolideos	Cancer	Leaves	Aqueous	Human ovarian cancer cell line and human keratinocyte cells – *in vitro*	(Stefanowicz-Hajduk, Justyna *et al.*, 2022)
	K. gracilis The Quercitina	Viral infection	Stem	Aqueous (Ethyl acetate and n-butanol fractions)	Enterovirus 71 and Coxsackievirus A16 strains in RD cells cultured in Eagle medium – *in vitro*; Intraperitoneal infection with Enterovirus 71 – *in vivo*	(Wang *et al.*, 2013)
	K. pinnata (unidentified)	Fungal infection in wounds	Leaves	Aqueous	Infection with *Candida albicans* in wounds – *in vivo*	(Zakharchenko *et al.*, 2017)

Source: The author

The genus presented a wide range of applications, this is linked to the chemical composition, where its secondary metabolites, such as flavonoids, polyphenols, bufadienolides, tannins, saponins, acids, alkaloids, exert important biological activities (Rivero-Pérez *et al.*, 2022; Stefanowicz-Hajduk *et al.*, 2022).

At work Chibli *et al* (2014), three anti-inflammatory flavonoids were identified: rutin, quercetin, and luteolin, which possibly reduce vasodilation, leukocyte infiltration, and edema. These compounds are antioxidants that prevent oxidative stress due to inflammatory processes. The anti-inflammatory activity of ethanolic extract of *K. pinnata* It can also be given by the presence of steroid derivatives. De Araújo *et al.* (2019) showed that aqueous extract of *K. brasiliensis* It can inhibit the inflammatory mediators released in the two phases of inflammation, showing better performance, while the *K. pinnata* It can inhibit only the mediators released in the first phase. They were able to reduce the activity of the cellular digestion enzyme, a result that suggests that the flavonoids present in the extract were able to inhibit the infiltration of neutrophils and consequently the response to inflammation. And Ferreira *et al.* (2014) corroborates, mentioning that flavonol, aglycone quercetin has an immunomodulatory effect through the regulation of inflammatory mediators.

In research *in vitro*, findings indicate that the ethanolic extract of *K. flammea* It induces the generation of oxidative stress when prostate cells are exposed, in which this cytotoxic action associated

with coumaric acid and palmitic acid present in the extract, which could lead to the activation of an apoptotic stimulus of the extract, inducing cell cycle arrest and antiproliferative activity (Arias-Gonzalez *et al.*, 2018). Another study shows that mitochondrial function was critically impaired by early apoptosis mediated by Kalantuboside B, a natural derivative of bufadienolid extracted from *K. tubiflora*, in melonoma cells *in vitro* (Hseu *et al.*, 2019; Huang *et al.*, 2013). And the study *in vivo* corroborated, showing the reduction of tumor size in mice (Hseu *et al.*, 2019). And Hsieh *et al.* (2016) has also had results where treatment *in vivo* It significantly slowed the growth of the lung tumor, with extract of the same species. Similar activity occurred with *K. Lativirens*, in which it exhibited significant antiproliferative effects against lung cancer cells (Kaewpiboon *et al.*, 2014).

Other compounds important in the antitumor activity of the genus *Kalanchoe* are the bulfadienolides, where they are usually characterized as toxic components with strong cytotoxic activity, among them are 16-hydroxybersaldegenin acetate; Bersaldegenin acetate-4 and 5; Bryophyllin A and B; Bersaldegenin acetate-1 and 2; Daigremontianina; and bersaldegenin-1,3,5-orthoacetate (Stefanowicz-Hajduk *et al*, 2020). Studies done with the species *K. daigremontiana*, show that the main bufadienolide, bersaldegenin-1,3,5-orthoacetate, has the potential to be responsible for the cytotoxic activity of the plant. Different types extracts showed strong antiproliferative and cytotoxic activities in ovarian cancer cells and significantly inhibited the cell cycle (Stefanowicz-Hajduk *et al.* 2022; Stefanowicz-Hajduk *et al.* 2020).

4 FINAL THOUGHTS

It is verified that the genus *Kalanchoe* is a potential botanical group in the treatment of several pathologies, namely: anti-inflammatory, antitumor, healing, antidiabetic, antiulcerogenic, antihypertensive, detrusor relaxant, neuroprotective, antiviral, antimicrobial, antiasthmatic, antitussive and nephroprotective action. Many secondary composites of plants of this genus, when used in adequate concentrations, have several medicinal effects.

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