Activity of *Kalanchoe pinnata* in Cancer

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Contributor: Marta Elena Hernández-Caballero , José Alfredo Sierra-Ramírez , Ricardo Villalobos-Valencia , Emmanuel Seseña-Méndez

Kalanchoe pinnata (Lam) Pers. (syn. *Bryophyllum pinnatum* Lam.), belonging to the genus Kalanchoe, is a succulent plant cultivated in gardens, which can be found as a herb or shrub. The bioactive ingredients in *Kalanchoe pinnata*, a succulent herb with ethnomedical applications for several diseases, including cancer, and reveal its anticancer mechanisms through a molecular approach.

Kalanchoe pinnata | phytochemicals | antitumor activity

1. Introduction

Cancer is a genetic disease that displays a variety of molecular alterations in the genome of somatic cells [1]. Cancer cells' traits, such as sustained proliferation, resistance to cell death, angiogenesis capacity, invasion, evasion of immune surveillance, and metastasis, could be the targets of bioactive compounds of medicinal plants. These alterations include small or large structural variations due to epigenetic changes characterized by the addition or removal of chemical groups from/to DNA, histones [2], or RNA [3]. As such, inherited or sporadic mutations cannot only activate oncogenes or deactivate tumor suppressor genes, but may even lead to reversible chemical modifications such as the methylation of DNA, histones, or RNA, which can affect gene expression without changing DNA sequences. Plants from the genus Kalanchoe (Fam: Crassulaceae) have a global distribution in warm climates, where they are used as ornamental plants. Some of the 200 Kalanchoe species are known for their curative uses in different diseases, including cancer. Natural remedies are used on a large scale worldwide, and herbal extracts are obtained from a great variety of plants. At the level of chemical composition, Kalanchoe species include flavonoids, bufadienolides, fatty acids, triterpenoids, alkaloids, phenolic acids, saponins, tannins, glycosides, and kalanchosides [4][5][6]; many of these constituents have remarkable anticancer potential. Numerous studies have evaluated the anticarcinogenic efficacy of these natural bioactive molecules. For example, quercetin has been reported to inhibit the proliferation of human breast cancer cells [7]. Bufadienolides have been shown to have antiangiogenic activity, cause inhibition of cell growth and proliferation, and induce cell death [8]. Antiproliferative activity has also been reported for triterpenes [9] and kalanchosides [5]. Important issues in cancer treatment are drug-related cumulative toxicity and chemoresistance. Hence, combination therapy offers good results due to the use of different targets and reduced adverse effects. Alternative therapy options may include the use of phytochemicals.

The features of *Kalanchoe pinnata* (**Figure 1**) and its phytochemicals, with a focus on the mechanisms underlying its chemopreventive and therapeutic properties.

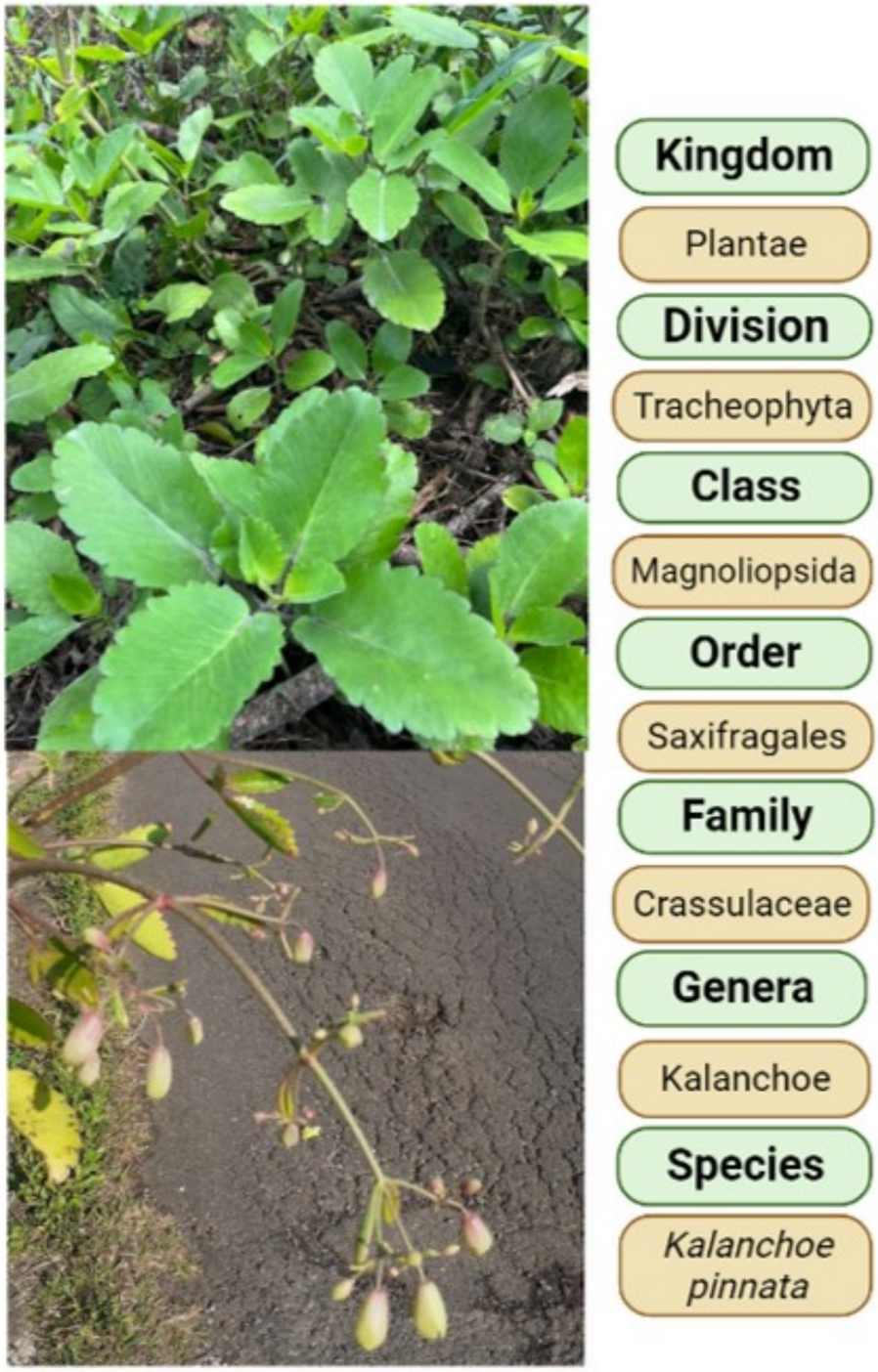

Figure 1. Taxonomic classification of K. pinnata. Source: Photos by researchers, image created with BioRender.com.

2. Phytochemical Constituents of *Kalanchoe pinnata*

Kalanchoe pinnata (Lam) Pers. (syn. *Bryophyllum pinnatum* Lam.), belonging to the genus Kalanchoe, is a succulent plant cultivated in gardens [10], which can be found as a herb or shrub. The plant has opposite, simple, and compound leaves, with a red to dark purple crenate margin. It reproduces from seeds and vegetatively through leaves [11], presenting clusters of reddish-purple pendulous flowers [12]. *K. pinnata* is used in traditional medicine to

treat different diseases including cancer [6]. Mora-Pérez and Hernández-Medel [13] analyzed the ingredients of *K. pinnata* and found alkaloids and sterols in methanolic root extract, and terpenes, sterols, flavonoids, chlorides, nitrates, and potassium in methanolic stem extract. The leaves of this plant contain phenols (gallic acid), flavonoids (quercetin) (in methanol extract), lycopenes, and β-carotenes (in petroleum ether) [14], as well as tannins and alkaloids [15]. Jaiswal et al. [16] found that the phenolic content of leaves was 28.4 ± 2 µg mg^{-1} and suggested that this was responsible for their antioxidant capacity. El Abdellaoui et al. [17] detected three phenolic acids (gallic, caffeic, and coumaric acids), three flavanol glycosides (quercetin, isorhamnetin, and kaempferol), 4′,5-dihydroxy-3′,8-dimethoxyflavone 7-O-β-D-glucopyranoside, and quercitrin [18]. Bufadienolides such as bersaldegenin acetate-2, -3, -4, -5, bryophyllin a, bryophyllin c, and bersaldegenin-1,3,5-orthoacetate [19] have also been found. Reported phenanthrene derivatives include Ψ-taraxasterol and 18-α-oleanane, and other ingredients include sterols; bryophynol, bryophyllol, and bryophollone [20]; stigmasterol [21]; campesterol, 24-epiclerosterol, (24R)-5α-stigmasta-7,25-dien-3β-ol, 5 α-stigmast-24-en-3β-ol, and 25-methyl-5α-ergost-24(28)-en-3β-ol [22] (**Figure 2**). The leaves of *K. pinnata* are rich in ascorbic acid (vitamin C) and contain riboflavin, thiamine, niacin, magnesium, calcium, potassium, phosphorus, sodium, and microelements such as iron and zinc [15]. *K. pinnata* flowers contain a higher concentration of glycosides [23], similar to other *Kalanchoe* species.

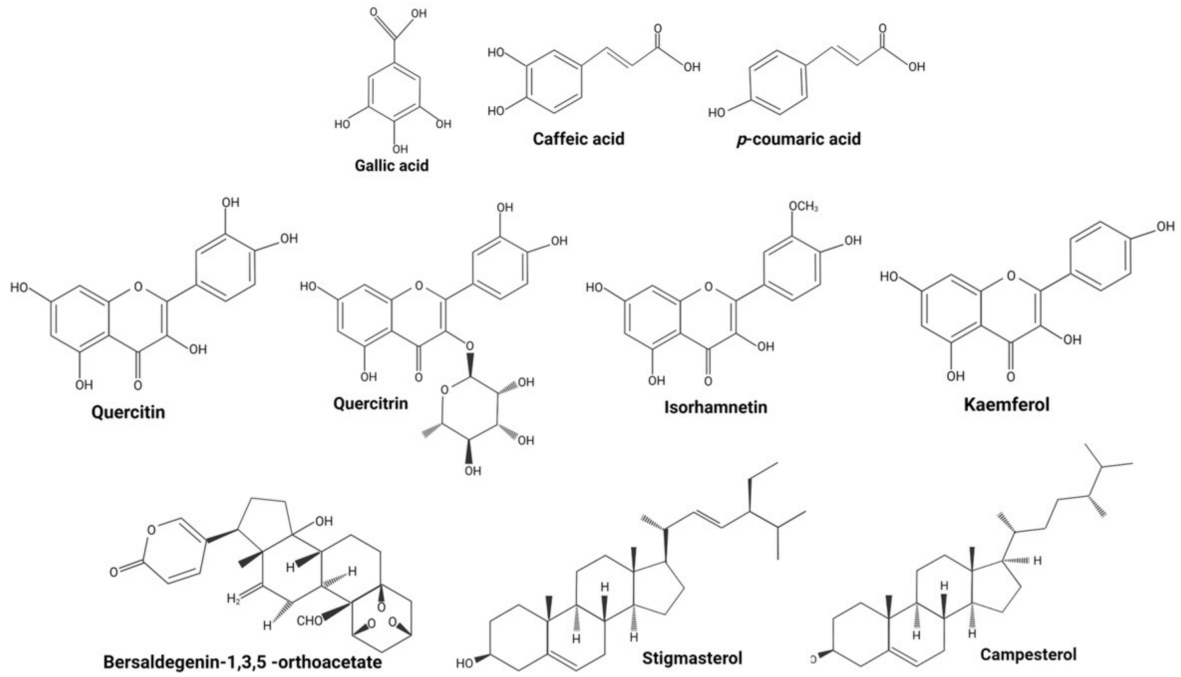

Figure 2. Structures of major phytochemicals reported in *K. pinnata*. Source: Image created with BioRender.com.

3. Activity of *Kalanchoe pinnata* in Cancer

Several plant components have been identified as sources of anticancer therapeutics. However, those components should be investigated in clinical trials to confirm their pharmacokinetic effects. Members of the Kalanchoe genus (Crassulaceae) have remedial properties for a wide range of diseases such as gastric ulcers, urolithiasis, bacterial, viral, and parasitic infections, skin diseases, cold, memory improvement, or even improvement in sleep quality

when undergoing cancer treatment. Based on ethnobotanical evidence, the Kalanchoe genus has been evaluated on various cancer cell lines (**Table 1**). The phytochemicals present in K. pinnata have been analyzed in a variety of studies on cancer.

Table 1. Anticancer properties found in the Kalanchoe genus.

Kalanchoe	Subject	Effect	Study Type	Cell Line	Reference
K. daigremontiana Raym.-Hamet and H. Perrier	Ovarian, cervical, breast cancer, and melanoma	Antiproliferative, cytotoxic, and antioxidant activity. Cell cycle arrest and caspase-independent cell death	In vitro	SCOV-3, HaCaT, HeLa, MCF-7, A375	[8][19][24][25][26]
K. integra var. crenata (Andr.)	Cardiotoxicity by doxorubicin Colorectal adenocarcinoma, lung cancer, mesothelioma, hepatocarcinoma, breast cancer	Cardio-protection against cardiotoxicity by cancer therapy Apoptosis	In vivo (rats) In vitro	DLD-1, A549, SPC212, HepG2, MCF-7	[9][27]
K. tubiflora (Harvey)	Lung cancer Lung adenocarcinoma, oral adenosquamous carcinoma, melanoma, and leukemia cell lines	Induction of autophagy Cell cycle arrest and senescence Cell cycle arrest and apoptosis Cytoprotective autophagy	In vitro In vitro, in vivo (mice)	CL1-5 A549, Cal-27, A2058, HL-60	[28][29][30]
K. gastonis-bonnieri Raym.-Hamet	Benign prostatic hyperplasia Prostate cancer	Antiproliferative activity and apoptosis induction Antiproliferative activity, apoptosis induction, and androgen receptor degradation	In vitro	Stromal cells LAPC-4, LNCaP, PC-3, DU145	[31][32]
K. flammea	Prostate cancer	Apoptosis induction and cell cycle arrest	In vitro	PC-3, LNCaP, PrEC	[33]
K. laetivirens	Lung cancer	Reversion of etoposide resistance	In vitro	A549, A549RT-eto	[34]

Kalanchoe	Subject	Effect	Study Type	Cell Line	Reference
K. gracilis (L.) DC	Murine macrophage and human hepatocarcinoma	Antiproliferative, antioxidant, and anti-inflammatory activity	In vitro	RAW264.7, HepG2	[35]
K. beharensis	Acute myeloid leukemia	Apoptosis induction, inhibition of NF-κB	In vitro	HL-60, HL60R	[36]
K. brasiliensis	Kidney carcinoma	Cytotoxic activity	In vitro	3T3, 786-0	[37]
K. laciniata	Baby hamster kidney cell line	Cytotoxic activity	In vitro in vivo (mice)	BHK-21	[38]

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yphenols,
which are widely distributed in plant tissues. These compounds are secondary metabolites produced for protection against bacteria, fungi, and insects. Natural phenols more studied for their properties are curcumin, epigallocatechin-3-gallate, resveratrol, quercetin, and myricetin [39], of these compounds, quercetin is found in *K. pinnata*.

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