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Review

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Biological properties of different extracts of the Kalanchoe daigremontiana ('Mother of thousands'): a review

Denise Carreiro Faustino[1], Naiara Nascimento das Chagas Lima[1], Kyan James Allahdadi[2,3] and Laise Cedraz Pinto[1,*]

[1]Department of Food Science, School of Nutrition, Federal University of Bahia (UFBA), Salvador, Bahia, Brazil,
[2]Center for Biotechnology and Cell Therapy, Monte Tabor, São Rafael Hospital, Salvador, Bahia, Brazil,
[3]D'Or Institute for Research and Education (IDOR), Botafogo, Rio de Janeiro, Brazil

*Correspondence: Laise Cedraz Pinto, Basílio da Gama Street, Canela Campus, 40301-110, Salvador Bahia, Brazil; Email: lcedraz@hotmail.com

Abstract

Objectives *Kalanchoe daigremontiana* (KD) is a succulent plant with widespread popular use as an anticancer and for the treatment of a variety of other diseases. The presence of bufadienolides (BFD), a cardiotoxic compound and other substances may justify some of its biological properties, however, clinical studies and toxicity and safety data are still scarce. The objective of this systematic review was to describe KD's biological properties and mechanisms, as well as its toxicity. Searches were performed in four databases with the descriptors: 'kalanchoe daigremontiana' AND 'cytotoxicity', 'antioxidant' OR 'anti-inflammatory' OR 'toxicity'. In total, 11 studies were included according to the PRISMA 2020 protocol.

Key findings The aqueous and ethanolic extracts of KD showed important antioxidant and anti-inflammatory activity, associated with the presence of flavonoids and phenols in the extracts. The extracts from fractions that were rich in BFD or dichloromethane showed anticancer (related to inhibition of mitochondrial dehydrogenase activity and reduction of glutathione level) and anticoagulant actions (due to reduced fibrin clot formation and increased degradation).

Summary More studies are still needed to demonstrate the concentration limits for beneficial effects and the toxic limitations of this species, until then, cautious use and consumption of KD is recommended.

Keywords: *Kalanchoe daigremontiana*; phenolics; bufadienolides; anticoagulant; cytotoxicity

Introduction

Plants are an important source of therapeutic substances[1] and can be used in the treatment of various diseases,[2] even though there has been a reduction of use due to the introduction of traditional medicine, based on pharmaceutically developed drugs that may be safer and more effective.[1] Many plants are widely used due to their reduced deleterious effects and also as a consequence of the decrease in the population's purchasing power and the lack of access to health, such as the widespread therapeutic use of *Kalanchoe daigremontiana* (*KD*) in North and South America.[1] *KD*, native to Madagascar and popularly known as '*Mother of thousands*', '*Aranto*' and '*Devil's backbone*', is a succulent plant that grows to a height of one and a half meters and is characterized as an invasive species as it alters the substrate where it is found[3] and can easily spread to other locations[4] (Figure 1).

Some biological properties of KD have already been reported in the literature, such as those exhibiting antidiabetic, antihistamine,[1] cardiotonic, anti-inflammatory, anticancer and antithrombotic effects.[5] Its leaves are widely used to treat infectious diseases of fungal, viral or bacterial origin, due to their antimicrobial and antifungal properties.[6] In popular medicine, there is an indication of the use of leaves in salads, juices and teas for the treatment of cancer, tumours and abscesses, hypertension, renal colic, diarrhoea, psychological diseases, gingivitis, ulcers and urinary infections. The leaves macerated in oil have demonstrated anti-inflammatory, antihaemorrhagic and astringent capabilities, while capsules containing plant extract have been used in the treatment of allergic rhinitis.[7]

Several compounds have been identified in KD, such as organic acids, steroids, flavonoids and glycosides, which explains most of its biological properties.[8] Among the substances reported, bufadienolides (BFD) are the most prominent, as they have cardiotonic activity due to the inhibitory mechanism of the sodium and potassium pump, which causes an increase in intracellular calcium and can lead to alterations in cardiomyocyte function.[5, 9] BFD also has an anticancer effect and has been widely studied for many years.[4] However, the studies are typically developed with BFD of animal origin (from the frog) so there is a need for further studies with BFD of plant origin, specifically present in KD, to confirm these properties, previously mentioned.

Therefore, identifying studies that show the concentration limits necessary for achieving beneficial effects and also identify potential toxic limitations is critical. In this context, the objective of the present review study was to describe the evidence on the biological properties and their mechanisms, as well as evidence of toxicity in KD.

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Figure 1 Photographic records of *K. daigremontiana* (*KD*). (A) *KD* grown in culture pots. (B) *KD* grown in soil. Author's registration.

Methods

This systematic review was performed by online searches of the following: Pubmed, Web of Science, ScienceDirect and Scopus databases. The descriptors 'kalanchoe daigremontiana' AND 'cytotoxicity', 'antioxidant' OR 'anti-inflammatory' OR 'toxicity' were used. The inclusion criteria were: clinical, in-vivo, in-vitro and in-silico studies published between 2016 and 2022. The search returned 172 articles and the preselection was made by reading the abstracts and titles of the articles for later full reading, while excluding review articles. This resulted in 11 articles that were included for full reading, according to the PRISMA 2020 protocol[10] (Figure 2). The main data of the study design and main results were described in tables.

Results and Discussion

Despite the popular use of KD leaves and extracts, studies that explain the mechanisms by which KD acts and its general properties remain limited. Studies selected for this review demonstrate that different extracts (ethanolic, aqueous, methanolic, hydroalcoholic or BFD fractions, for example) isolated from certain parts of KD, such as leaves and roots, showed antioxidant activity, antimicrobial activity, anticancer activity and important effects on the coagulation cascade, which are shown in Table 1 and are also described below.

Antioxidant activity

Kolodziejczyk-Czepas *et al.*[11] evaluated the antioxidant effect of the BFD-rich KD fraction extracted from KD roots on blood plasma proteins and lipids (Table 1). The authors observed a moderate antioxidant effect, occurring at concentrations of 50 µg/ml, while the trolox standard demonstrated effects at 5 µg/ml. In the lipid and protein components of plasma, the BFD-rich KD fraction reduced lipid hydroperoxides and TBARS, substances considered biomarkers of oxidative stress. This KD fraction protected against the oxidation of -SH protein groups, and tyrosine nitration and reduced blood plasma lipid peroxidation.

Navarrete *et al.*[1] demonstrated that the methanolic extract of KD leaves showed an important antioxidant activity, as there was a reduction of cellular liver damage when 2 ml of extract (juice) from crudes leaves was administered for 6 months in rats with a sucrose-rich diet (Table 1). Hyperglycaemia can lead to an elevation in levels of oxidative stress, which is linked to the pathogenesis of diabetes. When analysing the content of flavonoids and total phenols in the crude extract used, Navarrete *et al.*[1] identified a high content of these compounds, which is also fundamental in the fight against free radicals and has a protective effect against cardiovascular and inflammatory diseases (Table 1).

In the study by Báez *et al.*,[12] hydroalcoholic extracts were used to analyse the antioxidant and anti-inflammatory activity of KD. The highest amount of flavonoid and phenol was found in the ethanolic extract at 70%, indicating better extraction of these compounds in *KD* by the ethanol solvent. This justifies the fact that the 70% ethanolic extract (IC50 3.01 mg/ml) showed better antioxidant activity than the concentrations of 50 and 80% ethanol and 80% methanolic extract (Table 1).

Quintero *et al.*[3] evaluated the antioxidant effects of *Kalanchoe pinnata* and *KD* in ethanolic extract of aerial parts of plants and observed that in the model of DPPH uptake in both species, the maximum inhibitory effect was reached at 49.5% for the ethanolic extract of *K. pinnata* (at 2000 µg/ml) and 34% for the ethanolic extract of *KD* (at 1000 µg/ml). In this study, *KD* was more efficient as an antioxidant than *K. pinnata*. In this sense, the high content of phenolic compounds present in *KD* may justify the antioxidant activity of the plant, since phenols exhibit potent antioxidant activity (Table 1).

Bogucka-Kocka *et al.*[13] evaluated the required concentration of ethanolic extract (by maceration and accelerated extraction of KD leaves, each) to reduce 50% of free radicals under the conditions tested. The results showed that KD ethanolic crude extract eliminated 80% of the DPPH radicals at a concentration of 0.3 mg/ml, which is the third-best antioxidant species among the Kalanchoe species (Table 1).

Anti-inflammatory activity

Báez *et al.*[12] also investigated the anti-inflammatory activity of KD through its ability to inhibit the LOX enzyme that converts linoleic acid into lipid hydroperoxides. The results showed that the enzyme activity was reduced by 50% with a concentration of 21.96 µg/ml of the ethanolic extract of aerial parts of *KD* (Table 1). The authors discussed that, compared with other Kalanchoe species, *KD* demonstrated a potent anti-inflammatory effect.

Quintero *et al.*[13] also analysed the anti-inflammatory activity of aqueous extract and petroleum ether of *KD* and *K. pinnata*. The authors used ÿ-Carrageenan to induce paw inflammation and oedema (*in which animal model?). *KD* extracts showed an inhibitory effect on inflammation during

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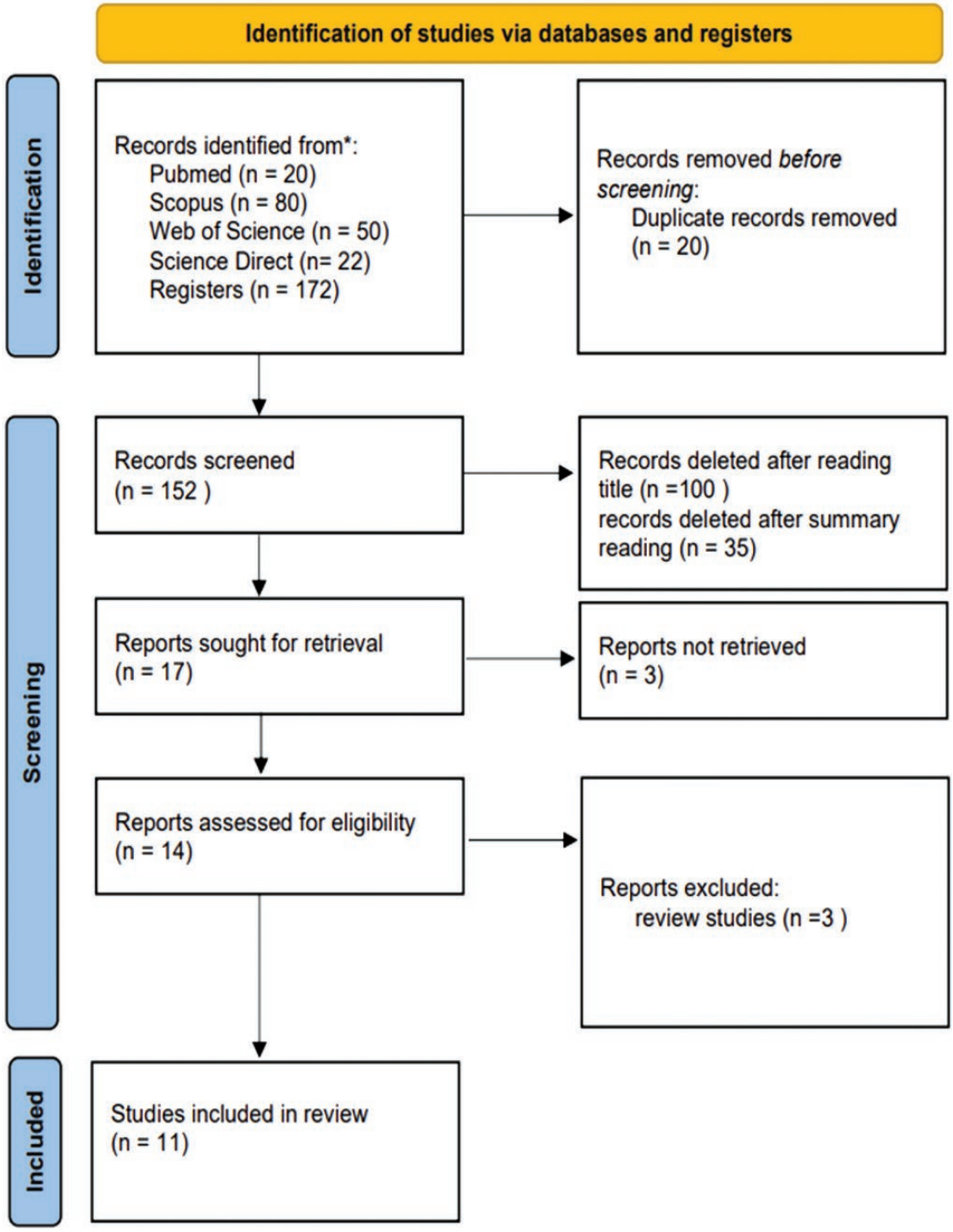


Figure 2 Selection of studies on biological and toxicological properties of KD according to PRISMA 2020.

the first 5–7 h, corresponding to the drug *diclofenac*, which is widely used to treat inflammation (Table 1). As the study evaluated aqueous and ethanolic extracts, it seems that the levels of phenols and flavonoids in *KD* may be directly involved in the observed anti-inflammatory effect.

Antimicrobial and antiparasitic activity

KD is widely used as a therapy for parasitic and viral diseases.[17] To understand the mechanisms and how this species acts on parasitic strains, Elizondo-Luévano *et al.*[14] evaluated the effect of methanolic extract of *KD* leaf on strains of *Entamoeba histolytica* and *Trichomonas vaginalis*, important parasites that directly impact public health. The inhibitory concentrations (IC50) of the crude *KD* extract against *E. histolytica* and *T. vaginalis* using the Probit test, were 70.71 and 105.27 μg/ml, respectively (Table 1). *KD* extract showed lower efficiency in antiprotozoal activity when compared with quercetin alone (IC50 of 44.48 and 21.17, respectively) and metronidazole (IC50 of 0.17 and 0.09 μg/ml, respectively). Despite this, the authors reported that the results are

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Table 1 Data from studies on the evaluation of KD extracts and main effects identified

Reference	KD extract	Highlight results
Antioxidant activity		
[11]	Methanolic extract (roots) rich in BFD	Moderate antioxidant effect at 50 µg/ml and reduction of lipid hydroperoxides and TBARS at 1–50 µg/ml.
[1]	Methanolic extract and crude juice (leaves)	Crude extract (juice) reduced hepatic oxidative damage in rats treated with 2 ml orally for 6 months. Extracts showed high content of flavonoids and total phenols.
[12]	Hydroalcoholic extracts (aerial parts)	Ethanolic extract (70%) showed greater antioxidant capacity in the DPPH assay compared with the other extracts.
[3]	Crude ethanolic extract (aerial parts)	Crude ethanolic extract at 1000 µg/ml reduced DPPH in 34%
[13]	Ethanolic extract (leaves)	Ethanolic crude extract eliminated 80% of the DPPH radicals at 0.3 mg/ml.
Anti-inflammatory activity		
[3]	Ethanol, aqueous and petroleum ether crude extract (leaves)	Ethanolic extract (62.5 µg/ml) showed greater anti-inflammatory action.
[12]	Hydroalcoholic extracts (aerial parts)	Ethanolic extract (50–80%) at 21.96 µg/ml (average) inhibited by 50% the activity of the LOX enzyme.
Antimicrobial and antiparasitic activity		
[14]	Methanolic extract (stem and leaves)	Methanolic extract showed IC50 antiparasitic activity of 70.71–105.27 µg/ml.
[15]	Aqueous and ethanolic extract (leaves)	Ethanol extract showed no significant toxic action against *Candida albicans* (minimum inhibitory concentration was >787 ug/ml)
Cytotoxic activity for cancer cells		
[4]	Aqueous, ethanolic and dichloromethane extract (leaves)	Dichloromethane fraction showed the strongest activity against all cell lines with IC50 ≤ 10 µg/ml
[15]	Aqueous and ethanolic extract (leaves)	Aqueous extract KD (14.39 µg/ml) exhibited more potent cytotoxic activity than the ethanolic (>100 µg/ml).
[13]	Ethanolic extract (leaves)	Ethanolic extract (359.4 µg/ml) demonstrated cytotoxic activity for human acute lymphoblastic T leukaemia cells
[16]	Aqueous extract (leaves)	In myeloma cell, aqueous extract (at 0.17 mg/well) inhibited viability by 13%, and (at 1.57 mg/ml) showed cytotoxicity by 47.8%. KD may act by inhibiting the activity of mitochondrial dehydrogenases and reducing glutathione levels.
Anticoagulant activity		
[9]	Aqueous extract (roots)	Aqueous extract at 25 and 50 µg/ml inhibited plasmin activity and reduced to 34.96 and 34.67%, respectively.
[5]	Methanolic extract (roots)	BFD-rich fraction at 50 µg/ml reduced thrombin amidolytic activity by 90%

KD, *Kalanchoe daigremontiana*; BFD, bufadienolides.

important for the understanding of the antiparasitic activity of *KD*, especially due to the supposed compounds in its extract that reduce the growth of protozoa.

In contrast, the Stefanowicz-Hajduk *et al.*[15] evaluated the action of KD on Candida albicans and demonstrated that the ethanol extract had no significant inhibitory action, with a high inhibitory concentration compared with other Kalanchoe species (>787 ug/ml) (Table 1). However, the aqueous extract was effective for *Candida albicans* and bacteria (*Streptococcus, Corynebacterium difteria, Staphylococcus aureus ATCC6538, Staphylococcus aureus MRSA ATCC43300, Enterococcus hirae ATCC10541, Escherichia coli ATCC8739*) tested at >50 ug/ml. Therefore, for microbiological purposes, this study demonstrated that the aqueous extract was more effective.

Cytotoxic activity for cancer cells

Studies on the cytotoxic activity of KD for cancer cells are still scarce, so Stefanowicz-Hajduk *et al.*[15] evaluated the effect of aqueous, dichloromethane and ethanolic extracts of KD on human adenocarcinoma cells, melanoma cell lines, breast and ovarian tumours (Table 1). The authors reported that the aqueous and ethanolic extracts (IC50 100 µg/ml) did not demonstrate significant cytotoxic activity in the cell lines used. However, the part extracted with dichloromethane showed more intense activity with IC50 ≤ 10 µg/ml for all cell lines. Cell death occurred after 24 h of treatment, demonstrating that dichloromethane extract exhibits significant differences in chemical composition when compared with the other extracts. The aqueous and ethanolic extracts showed a higher concentration of flavonoids, such as quercetin, glycosides and kaempferol, while the dichloromethane fraction is richer in BFD, mainly bersaldegenin-1,3,5-orthoacetate. This demonstrates that BFDs have cytotoxic potential against these cell lines, however, it should be noted that these compounds are also toxic to normal cells. Uncontrolled use of these compounds is associated with a high risk of dangerous side effects, especially cardiotoxicity. However, another study by Stefanowicz-Hajduk *et al.*[15] (Table 1) demonstrated that the aqueous extract of KD (14.83 µg/ml) was toxic to SKOV-3 cells (ovarian tumours), and is even more toxic than the ethanol extract (>100 µg/ml).

Akentieva *et al.*[16] evaluated the effects of *KD* and *Aloe arborescens* extracts on multiple myeloma cells, a serious

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Table 2 Cytotoxic or inhibition concentrations of various KD extracts in cells or systems

Reference	Cell or system	KD extract/ tested concentrations	Results
[11]	Platelets	BFD-rich fraction (1–50 µg/ml)	No cytotoxicity. 1–25 µg/ml did not induce an increase in LDH
[15]	Human ovarian cancer cells, cervical adenocarcinoma, malignant melanoma	Aqueous and ethanolic extract from leaves(<100 µg/ml)	No cytotoxicity
[14]	Human erythrocytes	Methanolic extract from leaves (50, 100, 200, 400, 600, 800, 1000 µg/ml)	Haemolysis at 1000 µg/ml
[12]	Lipoxygenase (LOX) inhibition assays	Ethanolic extract (50–80%)from leaves (tested concentrations not described)	Effects on enzymatic activity inhibition at CI_{50} 21.96 µg/ml (average)
[13]	Normal human T lymphocytes	Ethanol extract by maceration of KD leaves Ethanol extract by accelerated extraction of KD leaves (tested concentrations not described)	No cytotoxicity at 956.5 µg/ml No cytotoxicity at 844.9 µg/ml
[16]	Human multiple myeloma cells	Extrato aquoso da folha da KD (1.57 mg/ml)	Cytotoxicity at 1.57 mg/ml by 47.8%
[5]	Thrombin	BFD-rich fraction *KD* (1–50 µg/ml)	No effects on enzymatic activity at 1 µg/ml

KD, *Kalanchoe daigremontiana*; BFD, bufadienolides.

type of cancer, and identified that Aloe and KD extracts at 0.17 mg/well reduced tumour cells' viability by 46 and 13%, respectively (Table 1). The authors highlighted that *KD* and Aloe extracts act by inhibiting the activity of mitochondrial dehydrogenases and, thus, reducing the viability of tumour cells. Plant extracts induce oxidative stress in myeloma cells and reduce their level of glutathione, a substance that acts as a protective factor. Reducing the level of glutathione in cancer cells may be important in cancer chemotherapy, since glutathione contributes to resistance to various chemotherapy drugs. Based on this, KD extracts may perform well as it can implement two mechanisms of action against carcinogenesis.

Bogucka-Kocka *et al.*[13] evaluated in their work the ethanolic extract of KD leaves, which resulted in the extract exhibiting a cytotoxic effect for human acute lymphoblastic T leukaemia cells at concentrations of 359.4 µg/ml (Table 1). KD also demonstrated a cytotoxic effect for the normal lymphocyte lineage, however, the effect was only observed at higher concentrations (IC50 = 844.5 µg/ml).

Anticoagulant activity

KD was also evaluated in relation to its interaction with enzymes of the coagulation cascade. Kolodziejczyk-Czepas *et al.*[5] demonstrated that the plant fraction rich in BFD (1–50 µg/ml) reduced between 10 and 66% of the amidolytic activity of thrombin, an important enzyme that catalyses the conversion of fibrinogen to fibrin (Table 1). However, compared with the standard drug Argatroban (IC50 0.78 µg/ml), KD activity (IC50 2.78 µg/ml) was less efficient. The anticoagulant action occurred both on fibrinogen alone and on fibrinogen in blood plasma. The authors indicate that the compounds identified as possible non-competitive thrombin inhibitors present in the KD extract are bersaldegenin 1,3,5-orthoacetate, bersaldegenin 1-acetate, bersaldegenin, hovetrichoside C and daigredorigenin 3-acetate and schisandriside. In agreement with these results, another study by Kolodziejczyk-Czepas *et al.* (2018) demonstrated that the BFD-rich fraction increased the amidolytic action of plasmin (an enzyme that degrades fibrin clots) at lower concentrations (0.05–2.5 µg/ml) (Table 1). These data demonstrate that BFD can act as an anticoagulant in two ways: reducing fibrin clot formation and increasing its degradation.

On the other hand, higher concentrations (25–50 µg/ml) inhibited plasmin activity by about 60%, and also inhibited plasminogen activation. These results indicate that the action of BFD is dose-dependent in modifying the biological activity of plasmin, either stimulating or inhibiting, depending on the concentration used. Therefore, the activity of KD in relation to the coagulation cascade should be further investigated, to clarify what actions this fraction effectively promotes in these enzymes.

Effects on cell viability and/or cytotoxicity

KD extracts were tested in different cells and systems, such as blood platelets, human erythrocytes and proteins, including thrombin and plasmin as shown in Table 2.

Elizondo-Luévano *et al.* (2021) evaluated the effect of the methanolic extract from KD, where the plant has lower toxic activity, making it viable for use in disease treatments (Table 2). Quercetin extracted and isolated from *KD* did not show significant cytotoxicity, as well demonstrate highly cytoprotective actions.

Kolodziejczyk-Czepas *et al.*[11] studied, for the first time, the cytotoxic effects of the BFD-rich fraction isolated from *KD* on blood platelets *in vitro* through the release of lactate dehydrogenase from platelets. No cellular damage was identified that would suggest KD cytotoxicity at the tested concentrations of 1–50 µg/ml. Regarding the safety of the use of this extract, the cytotoxicity assays (Table 2) showed that concentrations up to 25 µg/ml did not induce an increase in LDH (a substance that indicates cell injury), whereas concentrations above 50 µg/ml increased 14%, but it was not statistically significant.

Bogucka-Kocka *et al.*[13] evaluated the cytotoxicity of the extract to normal human T lymphocytes. The maximum non-cytotoxic concentration of the ethanol extract used was 844.9 µg/ml (Table 2), a relevant range, since the action on cancer cells was effective at concentrations of 359.4 µg/ml, demonstrating that this extract within the parameters evaluated was safe.

Kolodziejczyk-Czepas *et al.*[5] evaluated that, for thrombin, at 1 µg/ml of the KD BFD-rich fraction was the maximum concentration that did not cause effects on enzymatic activity

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(Table 2), emphasizing that the enzyme was very sensitive to the inhibitory action of the extract.

Data on KD toxicity are still limited. KD is characterized as a promising species in relation to its biological properties, however, the evidence about its therapeutic effect still remains uncertain, requiring more robust clinical studies to concretely define its real applicability in clinical practice.

Conclusion

Biological properties evidenced in KD are related to different types of extracts, which characterize different chemical compositions that present specific properties. The aqueous and ethanolic extracts of KD showed important antioxidant and anti-inflammatory activity, while fractions that are rich in BFD or dichloromethane showed anticancer and anticoagulant action. KD extracts up to 844.9 µg/ml did not demonstrate cytotoxic activity in normal cells. More studies are still needed to show the concentration limits for the beneficial effects and the toxic limitations of this species.

The consumption of KD, whether as extracts, infusions, salads, juices, according to popular indications, requires cautious consumption, since no clinical studies were found that present guideline values for toxicity, thus, with the lack of scientific data to ensure the safety of its use, extreme caution must be applied. It is important to emphasize the need for better-designed studies to highlight the biological properties associated with the use of this species.

Author Contributions

Denise Carreiro Faustino and Naiara Nascimento das Chagas Lima performed the literature search, data analysis and writing—original draft preparation. Kyan James Allahdadi performed writing—review, editing and English review. Laise Cedraz Pinto performed conceptualization, writing—original draft preparation and writing—review.

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Conflict of Interest

The authors have no conflict of interest to declare.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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