Review

A Review of The Pharmacognostical and Pharmacological Properties of The *Kalanchoe* Plant as Treatment for Dermatological-Related Conditions

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ABSTRACT

The Kalanchoe genus is composed of more than 100 species that usually thrive in tropical environments, which have been used in folkloric medicine to treat various illnesses, including dermatological conditions. With this, the present study assesses the pharmacognostical and pharmacological properties of different species of the Kalanchoe genus as elements for a potential treatment for dermatological-related conditions, from findings of existing literature and studies. It was analyzed that the Kalanchoe pinnata plant, or one of the most common species of Kalanchoe, have been observed to have distinct morphological and microscopic characteristics. Further, it was discovered that different species of Kalanchoe have anti-inflammatory, antioxidant, antibacterial, and wound healing properties, which enable the plant to be used for dermatological products that are available to the market. With this, it is recommended that further studies be conducted in other understudied species of Kalanchoe regarding their pharmacological properties, as well as the use of other structures of the Kalanchoe plant for treatment of various dermatological conditions.

Keywords: Kalanchoe; antibacterial; anti-inflammatory properties; wound healing; antioxidant

INTRODUCTION

The *Kalanchoe* is a genus composed of more than 100 succulent plants that usually thrive in tropical environments. This genus was first reported by Michel Adanson, a French botanist, in the mid-1700s (Baldwin, 1938). The origin of the *Kalanchoe* genus is hypothesized in Madagascar, with the largest number of discovered species of the said genus found in the area. It is also suggested that the species of the genus are native to several areas in Asia, such as in Southeast Asia and China, southern and eastern Africa, and the Americas (Allorge-Boiteau, 1996). A synonym for this genus is *Bryophyllum*. The list below is the taxonomic classification of the genus for easy identification (Integrated Taxonomic Information System, n.d.).

Scientific Classification of Kalanchoe

Kingdom: Plantae

Subkingdom: Viridiplantae

Superdivision: Embryophyta

Division: Tracheophyta

Class: Magnoliopsida

Order: Saxifragales

Family: Crassulaceae

Genus: Kalanchoe

Different species of the genus have been used as folkloric medicine in different parts of the world. According to Kawade et al. (2014), species of the *Kalanchoe* have been employed in traditional medicine as treatment to alleviate various infections, fever,

and inflammation (Nayak et al., 2010). These were also used as a remedy for different respiratory illnesses (Biswas et al., 2011; Gulati et al., 2016), digestive illnesses (De Araujo et al., 2021), allergy (Cruz et al., 2012; Beigoli et al., 2021), and nausea (Majaz et al., 2011; Kawade et al., 2014). Further, different species of the *Kalanchoe* have been found to have antimicrobial (Akinpelu, 2000; Majaz et al., 2011), wound healing (Mahamood & Patil, 2002; Suprapto et al., 2011), and anti-ageing capabilities (Destandau et al., 2014).

With this in mind, the present study assesses the pharmacognostical and pharmacological properties of different species of the *Kalanchoe* genus as elements for a potential treatment for dermatological-related conditions, using existing literature and studies. It is hypothesized that the anti-inflammatory, antioxidant, antibacterial, and wound healing properties of different species of *Kalanchoe* are necessary for the formulation of treatment on several dermatological illnesses, such as acne and eczema.

PHARMACOGNOSTICAL ANALYSIS OF KALANCHOE

Multiple studies were conducted to discover and observe the macroscopic and microscopic characteristics of *Kalanchoe pinnata*, one of the most common species of the *Kalanchoe* genus.

Morphological Characteristics

Usually, *Kalanchoe pinnata* has a height of between 0.3 to 1.2 m, with other occurrences of 2 m height. The stem changes color, depending on its age. Older stems are characterized as light colored, while younger stems are usually reddish with white speckles. Also, the stems are usually branched and smooth, which are also tall and hollow.

The flowers of *Kalanchoe pinnata* are colored pinkish red, and are characterized as soft and tubular. These are hanging in large panicles and opposite stout branches. Further, the corolla are usually swollen and shaped octagonal at the base. The calyx of the flower can be observed to be tubular and brownish or purplish in color, which can be 3.5 to 4 cm long. The base of the flower is usually colored pale green, and has triangular teeth.

Meanwhile, the leaves have an ovate or elliptical shape, and a crenated or serrated leaf margin. The leaves also contain an asymmetric base, a glabrous leaf surface, and a long petiole. In addition, the color of the leaves depend on the side of the epidermis, i.e., upper epidermis are usually colored dark green while lower epidermis are usually lighter. The leaves are also characterized with a distinct odor and having a bitter taste.

The fruit of the *Kalanchoe pinnata* plant are usually enclosed by the calyx and corolla that are characterized as papery. Moreover, the seeds of the species are distinguished as smooth and oblong-shaped (Majaz et al., 2011; Kawade et al., 2014; Shruti et al., 2018).

Microscopic Characteristics

The lamina of the leaf of the *Kalanchoe pinnata* contains a layer of epidermis, hypodermis, palisade cells, and meristele which passes through the midrib that exposes the collenchymatous tissues, both sides of the epidermis, meristele, and the vascular bundle. This space is characterized as flat and even. The trichomes are absent in the adaxial and abaxial sides of the leaf. The leaves are also observed to be shallow on the adaxial, and convex on the abaxial side.

The ground tissue of the midrib is composed of parenchyma cells and are homogeneous. The parenchymatous cells are compact and are circular in shape. Meanwhile, the vascular strand is hemispherical in shape, consisting of horizontal bands of xylem and wide bands of phloem. The vascular strands comprise the vascular bundles, which can be at least $170 \mu m$ in diameter in a horizontal plane.

In addition, the leaf petiole contains calcium oxalate crystals found in parenchymatous cells, with spiral vessels being observed in the area. Further, the stomata of the leaf of *Kalanchoe pinnata* is also observed. It was discussed that there are many

stomata present in the leaf at approximately 18 to 20 per mm of length. The stomata of the leaf is described as anisocytic, or structures that are uneven in size (Gracie, 2018).

In terms of the stem, it is observed that there is a cuticle covering the thick-walled epidermis as its outer layer. Beneath this outermost layer is the hypodermis, which is composed of sclerenchymatous cells. Further, the cortex of the stem is made up of loosely arranged parenchymatous cells that are characterized by its thin walls and starch grains.

The xylem of the stem is similar to the characteristics of the herbaceous dicots, i.e., usually in the form of tracheids with some parenchymal fibers. Meanwhile, the pith of the stem of the species is characterized by the deposition of starch grains and crystals made from calcium oxalate (CaC_2O_4), and is composed of parenchymatous cells.

The flowers of the *Kalanchoe pinnata* are noticed to have both sides of the epidermis, composed of spongy cells and pigments which determines the color of the plant's flower. (Majaz et al., 2011; Kawade et al., 2014; Shruti et al., 2018; Shaheer et al., 2019).

PHARMACOLOGICAL PROPERTIES OF KALANCHOE CONCERNING DERMATOLOGY

Existing studies regarding various pharmacological properties of different species of *Kalanchoe pinnata* have been performed, which can be used in the present study to analyze how these properties can be used as properties for different dermatological properties that can be used as possible treatment for various dermatological conditions.

Anti-Inflammatory Properties

According to multiple studies, the leaves of *Kalanchoe pinnata* have been found to have anti-inflammatory cavities which have been seen to reduce the formation of edema and accumulation of fluid (Parveen et al., 2007; Ferreira et al., 2014; Andrade et al., 2020). This capability of the *Kalanchoe pinnata* to significantly reduce the damage in macroscopic and microscopic levels. Further, there are *in vivo* studies which found that various structures of the plant have been found to lessen the effect of inflammatory diseases (Nascimento et al., 2018; Fernandes et al., 2017; Andrade et al., 2020). Another study has been found that *Kalanchoe pinnata* can be used to decrease inflammation among diabetic feet (Cawich et al., 2014).

It was also revealed that extracts from the leaves of the *Kalanchoe pinnata* have been found to reduce the synthesis of enzymes that were known to induce inflammation, i.e., phospholipase A₂, cyclooxygenase, and PGE synthase. This would also reduce the expression of various symptoms of inflammation, such as pain, heat, and redness. (Mancini & Batista, 2011; Ferreira et al., 2014).

Antioxidant Properties

The extracts of the leaf of various species of the *Kalanchoe* genus have been found by various studies to have antioxidant properties. Destandau et al. (2014) stated that the flavonoids obtained from the methanolic extract of the leaf of *Kalanchoe pinnata* have antioxidant activity in most of human's keratinocyte cells. The keratinocytes are responsible for skin aging, which can be induced due to oxidative stress and inflammation (Jenkins, 2002; Chung et al., 2009; Destandau et al., 2014).

Further, a similar study by De Araujo et al. (2018) stated that the juices from the leaves of *Kalanchoe brasiliensis* and *Kalanchoe pinnata* have increased the antioxidant defense system of the body, and have also contributed to decreased inflammation.

Antibacterial Properties

The extracts of various *Kalanchoe* species have also been found with antibacterial and antimicrobial properties. An experiment derived for a study by Stefanowicz-Hajduk et al. (2020) used extracts from the leaves of three species from the *Kalanchoe* genus to test their antimicrobial activity. It was found that *Kalanchoe daigremontiana* contain antimicrobial activity

(Nahar et al., 2008; Stefanowicz-Hajduk et al., 2008). Further, ethanolic extracts from *Kalanchoe blossfeldiana* have been found to have significant effect against bacteria, including *Corynebacterium diphtheria*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Enterococcus hirae*.

Further, new studies show that other species of *Kalanchoe* have been found to have antibacterial properties. Richwagen et al. (2019) discovered that *Kalanchoe fedtschenkoi* and *Kalanchoe mortagei* contain antibacterial activity against strains of bacteria that are characterized as resistant to drugs.

Wound Healing Activity

Many species of the *Kalanchoe* plant have been observed to have wound healing capabilities. The methanolic extract from the leaf of a *Kalanchoe pinnata* has been found to accelerate the time for wound healing (Suprapto et al., 2015). A different study from Mahamood et al. (2002), as cited by Majaz et al. (2011), stated that the water extract from the same species has been found to fasten the healing process among open wounds. Further, the same study have also discovered that other extracts from the leaf, i.e., a petroleum ether extract and an alcoholic extract, have increased the healing of incision wounds.

Further, a formulation containing leaves of *Kalanchoe petitiana A. Rich* have been observed to have significant wound healing capability in excision and incision models (Mekonnen et al., 2012). The methanolic and aqueous extracts of the leaf have also been found with increased wound contraction and the strength against skin breaking. Meanwhile, histological analysis has been found that *Kalanchoe pinnata* shows a positive effect on the collagen matrix remodeling and the repairing and subsequent epithelization of the wounds (Zakharchenko et al., 2017).

USE OF KALANCHOE PLANT IN DERMATOLOGICAL PRODUCTS

Because of the pharmacological properties stated in different studies, various species of the *Kalanchoe* genus have been used by researchers as the plant used for preparation and formulation of different dermatological and cosmetic products that are available in the market.

A study conducted by Pattewar & Patil (2014) displayed the evaluation of a formulation of an antiseptic cream made from the leaves of *Kalanchoe pinnata* as antibacterial. Researchers extracted 60% methanol by grounding the leaves for a week and concentrating the extracts through evaporation (Yanthi et al., n.d.; Majaz et al., 2011). Using the formulation, the researchers tested its minimum bactericidal concentration (MBC), or the lowest amount of antibacterial agent necessary to be able to kill a bacterium, against *Staphylococcus aureus*. It was found that the MBC against the aforementioned bacterium is at 30mg. Further, it was found that the antiseptic cream is non-irritant and has antimicrobial activity (Pattewar, Patil & Dahikar, 2013).

Another study has also evaluated a topical formulation containing extracts from species, *Kalanchoe brasiliensis* and *Kalanchoe pinnata* (De Araujo et al., 2019). The researchers generated an extract of the said species by drying the aqueous extracts and dissolving the dry extracts in distilled water. It was found that this formulation has the ability to decrease inflammation (Mourao et al., 1999; De Araujo et al., 2019), as researchers observed the decrease in enzyme activity of myeloperoxidase, which inhibits the inflammation of the skin (Jorch & Kubes, 2017).

Lastly, a study by Nayak, Marshall & Visitor (2010) showed that a formulation containing ethanol from the leaves of *Kalanchoe pinnata* has been found to have greater wound healing capabilities (86 percent) over other products, i.e., petroleum jelly, by at least 20 percent. Further, the formulation has been observed to have increased wound contraction and higher amount of hydroxyproline. These findings have been accepted by a different study which showed a similar wound healing capability of a formulation using the extract of the same species, albeit nine percent higher than the original study (Coutinho et al., 2020).

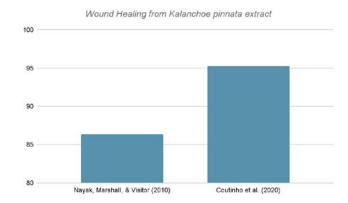


Figure 1. Comparison of the wound healing percentage of *Kalanchoe pinnata* extract from data by Nayak, Marshall & Visitor (*left*) and Coutinho et al. (*right*)

With this in mind, a study conducted by Mans & Grant (2017) stated that leaf extracts of *Kalanchoe pinnata* have been used as treatment for warts, prevention for acne and eye bags, and for skin regeneration. Further, it was also found that the pharmacological properties stated in the previous section have been the basis of the use of *Kalanchoe pinnata* as cosmetic products for wrinkles, acne, rashes, and sores (El Abdellaoui et al., 2010; Akpuaka & Ezem, 2011; Mans & Grant, 2017).

CONCLUSION

The species under the *Kalanchoe* genus have been used in folkloric medicine as remedy and treatment for different illnesses and diseases, including dermatological conditions. With this, the present study used findings from existing literature to assess the pharmacological and pharmacognostical properties of different species of *Kalanchoe* that can be used in the formulation of dermatological products in the market.

The pharmacognostical analysis of the *Kalanchoe pinnata*, one of the most common species of the *Kalanchoe* plant, observed the distinct morphological and microscopic characteristics of the species that allowed for easy identification of the said plant.

The pharmacological analysis of different species of the *Kalanchoe* plant, such as *Kalanchoe pinnata*, *Kalanchoe brasiliensis*, *Kalanchoe daigremontiana*, *Kalanchoe blossfeldiana*, *Kalanchoe fedtschenkoi*, *Kalanchoe mortagei*, and *Kalanchoe petitiana A. Rich*, has concluded that there are four properties that should be analyzed in formulating dermatological products, which include anti-inflammatory, antioxidant, and antibacterial properties, as well as wound healing capabilities. The mentioned pharmacological properties were key factors in the formulation of dermatological products made from extracts derived from the leaves of *Kalanchoe* plants.

With these conclusions drawn, it is recommended that further studies be conducted on other species of *Kalanchoe* that are understudied to assess their pharmacological properties. Also, it should be suggested that studies be conducted on the use of other structures of the *Kalanchoe* plant, such as the roots and stems, for the extracts in the formulation of dermatological products that would treat various dermatological conditions.

REFERENCES

- Allorge-Boiteau, L. (1996). MADAGASCAR CENTREDE SPECIATION ET D'ORIGINE DU GENRE KALANCHOE (CRASSULACEAE). Biogéographie de Madagascar, 1996, 137–145. https://horizon.documentation.ird.fr/exl-doc/pleins_textes_6/colloques2/010008454.pdf
- Andrade, A. W. L., Guerra, G. C. B., de Souza Araújo, D. F., de Araújo Júnior, R. F., de Araújo, A. A., de Carvalho, T. G., Fernandes, J. M., Diez-Echave, P., Hidalgo-García, L., Rodriguez-Cabezas, M. E., Gálvez, J., & Zucolotto, S. M. (2020). Anti-Inflammatory and Chemopreventive Effects of *Bryophyllum pinnatum* (Lamarck) Leaf Extract in Experimental Colitis Models in Rodents. *Frontiers in Pharmacology*, 11. https://doi.org/10.3389/fphar.2020.00998
- Baldwin, J. T. (1938). KALANCHOE: THE GENUS AND ITS CHROMOSOMES. American Journal of Botany, 25(8), 572–579. https://doi.org/10.1002/j.1537-2197.1938.tb09263.x
- Cawich, S. O., Harnarayan, P., Budhooram, S., Bobb, N. J., Islam, S., & Naraynsingh, V. (2014). Wonder of Life (kalanchoe pinnata) leaves to treat diabetic foot infections in Trinidad & Tobago: a case control study. *Tropical Doctor*, 44(4), 209–213. https://doi.org/10.1177/0049475514543656
- Coutinho, M. A. S., Casanova, L. M., Nascimento, L. B. D. S., Leal, D., Palmero, C., Toma, H. K., dos Santos, E. P., Nasciutti, L. E., & Costa, S. S. (2020). Wound healing cream formulated with Kalanchoe pinnata major flavonoid is as effective as the aqueous leaf extract cream in a rat model of excisional wound. *Natural Product Research*, *35*(24), 6034–6039. https://doi.org/10.1080/14786419.2020.1817012
- Cruz, E., Reuter, S., Martin, H., Dehzad, N., Muzitano, M., Costa, S., Rossi-Bergmann, B., Buhl, R., Stassen, M., & Taube, C. (2012). Kalanchoe pinnata inhibits mast cell activation and prevents allergic airway disease. Phytomedicine, 19(2), 115–121. https://doi.org/10.1016/j.phymed.2011.06.030
- De Araújo, E. R. D., Félix-Silva, J., Xavier-Santos, J. B., Fernandes, J. M., Guerra, G. C. B., de Araújo, A. A., Araújo, D. F. D. S., de Santis Ferreira, L., da Silva Júnior, A. A., Fernandes-Pedrosa, M. D. F., & Zucolotto, S. M. (2019). Local anti-inflammatory activity: Topical formulation containing Kalanchoe brasiliensis and Kalanchoe pinnata leaf aqueous extract. Biomedicine & Pharmacotherapy, 113, 108721. https://doi.org/10.1016/j.biopha.2019.108721
- De Araújo, E., Guerra, G., Araújo, D., de Araújo, A. A., Fernandes, J. M., de Araújo Júnior, R. F., da Silva, V. C., de 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. *International journal of molecular sciences*, 19(5), 1265. https://doi.org/10.3390/ijms19051265
- Destandau, E., Krolikiewicz-Renimel, I., el Abdellaoui, S., Cancellieri, P., Fougère, L., Toribio, A., Landemarre, L., André, P., & Elfakir, C. (2014). Bio-Guided Targeting for Preservative and Anti-Ageing Cosmetic Ingredient Development. *Cosmetics*, *1*(1), 14–28. https://doi.org/10.3390/cosmetics1010014
- Fernandes, J. M., Félix-Silva, J., da Cunha, L. M., Gomes, J. A. D. S., Siqueira, E. M. D. S., Gimenes, L. P., Lopes, N. P., Lira Soares, L. A., Fernandes-Pedrosa, M. D. F., & Zucolotto, S. M. (2017). Correction: Inhibitory Effects of Hydroethanolic Leaf Extracts of Kalanchoe brasiliensis and Kalanchoe pinnata (Crassulaceae) against Local Effects Induced by Bothrops jararaca Snake Venom. PLOS ONE, 12(2). https://doi.org/10.1371/journal.pone.0172598
- Ferreira, R. T., Coutinho, M. A. S., Malvar, D. 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. *Evidence-Based Complementary and Alternative Medicine*, 2014, 1–8. https://doi.org/10.1155/2014/429256
- Gracie, C. A. (2018, November 19). Anisocytic stomata. The William & Lynda Steere Herbarium. http://sweetgum.nybg.org/science/glossary/glossary-details/?irn=3209
- Integrated Taxonomic Information System. (2011). Kalanchoe Adans. Integrated Taxonomic Information System Report. https://www.itis.gov/servlet/SingleRpt/SingleRpt/search_topic=TSN&search_value=500355#null
- Kawade, R. M., Ghiware, N. B., Ghante, M. H., Malwatkar, S. M., Valvadkar, S. M., Dhadwe, A. K., & Choudary, R. V. (2014). A Review On Pharmacognostical, Phytochemical and Pharmacological Potentials of Kalanchoe pinnata (Crassulaceae). American Journal of Pharmtech Research, 4(1), 1–15. https://www.researchgate.net/publication/281858128 A Review On Pharmacognostical Phytochemical and Pharmacoglogical Potentials of Kalanchoe pinnata Crassulaceae
- Majaz, Q., Tatiya, A. U., Khurshid, M., Nazim, S., & Siraj, S. (2011). The miracle plant (Kalanchoe pinnata): A phytochemical and pharmacological review. International Journal of Research in Ayurveda and Pharmacy, 2(5), 1478–1482. https://www.researchgate.net/publication/268347927_The_miracle_plant_Kalanchoe_pinnata_A_phytochemical_and_pharmacological_review
- Mekonnen, A., Sidamo, T., Asres, K., & Engidawork, E. (2013). In vivo wound healing activity and phytochemical screening of the crude extract and various fractions of Kalanchoe petitiana A. Rich (Crassulaceae) leaves in mice. *Journal of Ethnopharmacology*, 145(2), 638–646. https://doi.org/10.1016/j.jep.2012.12.002
- Mourão, R. H. V., Santos, F. O., Franzotti, E. M., Moreno, M. P. N., & Antoniolli, A. R. (1999). Antiinflammatory activity and acute toxicity (LD50) of the juice of Kalanchoe brasiliensis (comb.) leaves picked before and during blooming. Phytotherapy Research, 13(4), 352–354. https://doi.org/10.1002/(sici)1099-1573(199906)13:4

- Nayak, B. S., Marshall, J. R., & Isitor, G. (2010). Wound healing potential of ethanolic extract of Kalanchoe pinnata Lam. leaf--a preliminary study. Indian Journal of Experimental Biology, 48(6), 572–576. https://pubmed.ncbi.nlm.nih.gov/20882759/
- Pattewar, S. V., & Patil, D. N. (2014). Formulation of herbal antibacterial cream by using extract from Kalanchoe pinnata leaves. Research Journal of Topical and Cosmetic Science, 5(1). https://rjtcsonline.com/AbstractView.aspx?PID=2014-5-1-1
- R.A. Mans, D., & Grant, A. (2017). "A thing of beauty is a joy forever". Plants and plant-based preparations for facial care in Suriname. *Clinical and Medical Investigations*, 2(4). https://doi.org/10.15761/cmi.1000143
- Richwagen, N., Lyles, J. T., Dale, B. L. F., & Quave, C. L. (2019). Antibacterial Activity of Kalanchoe mortagei and K. fedtschenkoi Against ESKAPE Pathogens. *Frontiers in Pharmacology*, 10. https://doi.org/10.3389/fphar.2019.00067
- Shruti, B., Bhavita, D., Maitreyi, Z., & Divya, C. (2018). A comparative pharmacognostical and phytochemical analysis of Kalanchoe pinnata (Lam.) Pers. leaf extracts. Journal of Pharmacognosy and Phytochemistry, 7(5), 1519–1527. https://www.researchgate.net/publication/328063857_A_comparative_pharmacognostical_and_phytochemical_analysis_of_Kalanchoe_pinnata_Lam_Pers_leaf_extracts
- Stefanowicz-Hajduk, J., Hering, A., Gucwa, M., Hałasa, R., Soluch, A., Kowalczyk, M., Stochmal, A., & Ochocka, R. (2020). Biological activities of leaf extracts from selected Kalanchoe species and their relationship with bufadienolides content. *Pharmaceutical Biology*, *58*(1), 732–740. https://doi.org/10.1080/13880209.2020.1795208
- Suprapto, A. K., Tih, F., & Evacuasiany, E. (2015). Effect of Methanolic Extract in Ointment and Powder of Kalanchoe Pinnata (Lamk) Leaf in Ointment towards Incision Wound Healing in Mice. *Journal Of Medicine & Health*, I(1).https://doi.org/10.28932/jmh.v1i1.495
- 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. *Journal of Immunology Research*, 2017, 1–9. https://doi.org/10.1155/2017/3940743