Jurnal Ilmiah Farmasi (Scientific Journal of Pharmacy) 20(1) Januari-Juli 2024, 31-42
ISSN: 1693-8666
available at http://journal.uii.ac.id/index.php/JIF

Begonia medicinalis: a review of phytochemistry and pharmacology

Levana Velincia Tanriono[1], Farida Hayati[2*], Muhammad Sulaiman Zubair[3]

[1,2] Department of Pharmacy, Universitas Islam Indonesia, Yogyakarta, Indonesia
[3]Department of Pharmacy, Faculty of Sciences, Tadulako University, Kampus Bumi Tadulako, Palu, Indonesia
**Corresponding author*: farida.hayati@uii.ac.id

Abstract

Background: *Begonia medicinalis*, often referred to as benalu batu, is a plant belonging to the Begoniaceae family. It is renowned for its wide range of pharmacological activities and its extensive application in the treatment of many diseases. Saponins, tannins, flavonoids, phenolics, steroids, alkaloids, and triterpenoids are some of the chemical compounds in this plant responsible for its pharmacological activity.

Objective: The aim of this review is to provide information about the phytochemical and pharmacological properties of *B. medicinalis*.

Method: This narrative review was performed by conducting literature searches on various relevant reputable online databases, and there were 17 articles that discussed the phytochemistry and pharmacology activity of *B. medicinalis*.

Results: People have long used *B. medicinalis* as a test treatment for a variety of diseases. Flavanols, 2-O-β-glucopyranosyl cucurbitan D, β-sitosterol-3-O-β-D-glucopyranoside, and 9(11)α,16(17)α-dioxirane-20,25-dihydroxy-β-sitosterol-3-O-β-glucopyranoside are among the compounds found in the plant. Studies have demonstrated the immunomodulatory, anticancer, antiviral, and antioxidant activity of this plant. *In vitro* toxicity tests revealed that this plant is toxic and has anticancer potential. The *in vivo* toxicity test revealed that this plant has mild toxicity.

Conclusion: This study suggests that *B. medicinalis* has strong potential for future development into herbal medicine.

Keywords: *Begonia medicinalis, Begonia sp.,* pharmacological, phytochemical

1. Introduction

Since the beginning of time, people have used plants as medicine. According to the World Health Organization (WHO), 80% of the world's population uses herbal medicines for health care. While the third-largest potential producer of medicinal plants in the world is Indonesia (Affandi & Batubara, 2019). With approximately 1870 species found worldwide, including in Indonesia, the Begoniaceae is the sixth-largest flowering plant genus (Moonlight *et al*., 2018). About ten plant species from this family have been studied for their chemical compounds and pharmacological activities (Zubair *et al*., 2020).

Benalu batu (*Begonia medicinalis*) is a species of the Begoniaceae family, particularly endemic to the Morowali district, Central Sulawesi, Indonesia. Based on previous studies of phytochemical identification, it contains saponins, tannins, flavonoids, polyphenols, alkaloids, steroidal glycosides, and pentacyclic triterpenoids (Anam *et al*., 2014; Khumaidi *et al*., 2020; Zubair *et al*., 2016). People in communities use *B. medicinalis* to treat diseases such as cancer,

diabetes, dry cough, fever, gout, kidney, laxatives, tumors, ulcers, urinary stones, worms, and others (Anam *et al*., 2014; Ardi *et al*., 2019; Herik, 2009; Zubair *et al*., 2020).

The pharmacological activities of this plant have also been reported, such as immunomodulatory (Syamsidi *et al*., 2023; Zubair, *et al*., 2022a; Zubair, *et al*., 2022b), cytotoxic (Anam *et al*., 2014; Prihardina & Fatmawati, 2021; Zubair *et al*., 2020), antiviral, antioxidant activity (Zubair *et al*., 2021), and the ability to reduce blood sugar and creatinine levels in the blood (Alaydrus, 2020; Tandi *et al*., 2020). In addition, a toxicity study *in vivo* resulted in a high LD_{50} value corresponding to safety profile (Putra, 2020). Thus, this study briefly highlighted recent scientific discoveries and provided a list of subjects requiring further research.

2. Method

This article reviewed research on the phytochemical and Pharmacological data of *B. medicinalis*, focusing on important information related to chemical composition, pharmacological studies, mechanisms of action, and toxicology. This narrative review was carried out by conducting literature searches on various journal websites, such as Google Scholar, PubMed, Science Direct, Web of Science, and others, and then tailoring the results to the research title, abstract, and keywords. For example, "*Begonia medicinalis*," "*Begonia sp.*", "phytochemistry," and "pharmacology" are the keywords used. As long as the published data is relevant to this review, there is no time limit for research in this article. The collected literature was then analyzed based on each study's methods, samples, results, and conclusions.

3. Result and discussion

3.1 Plant description

Begonia medicinalis (Figure 1) is a species in the Begoniaceae family. The word "medicinalis" refers to the use of this plant as a traditional medicine in Central Sulawesi. This plant, also known as Polohi Wasu, is an endemic plant found in Wawopada village, Morowali district, Central Sulawesi. It grows in shady and humid areas between large rocks because of its habitat in the primary tropical rainforest at 700 m above sea level. *B. medicinalis* is a perennial, monocotyledonous, erect, up to 30 cm tall, with a dense multicellular indumentum, trichomes up to 2 mm in size, and microscopic glandular hairs on stems and leaves. The stems branched with internodes 2–5 cm long and brownish. Leaves are pale green and elliptical, with a slightly

protruding midrib and an acuminate apex up to 5 mm long. Flowers are a protogynous compound. Female flowers compound with one male basal node; two-flowered or solitary female flowers; peduncle 1-5 mm long; hairy. Fruit stalks are 1–5 mm long, and unknown seed (Ardi *et al*., 2019).

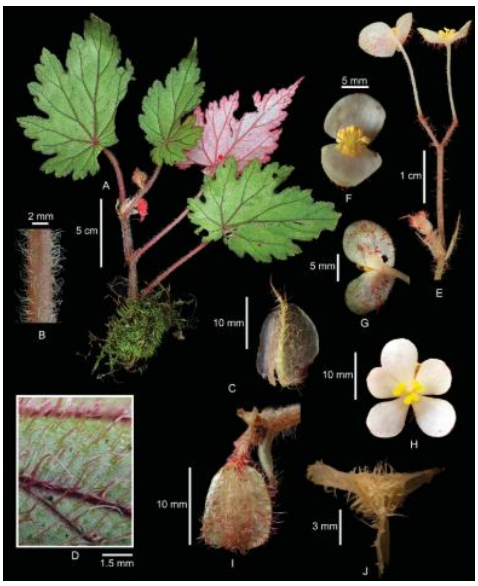


Figure 1. *Begonia medicinalis* (Ardi *et al*., 2019)

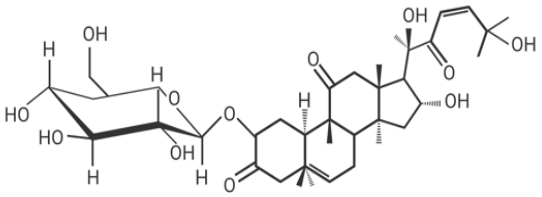
3.2 Traditional use

B. medicinalis is a multipurpose plant that has been used for centuries to treat diseases such as asthma, cancer, diabetes, dry cough, fever, gout, goiter, irregular menstruation, kidney, laxatives, lumbago, malaria, paralysis symptoms, rheumatism, tuberculosis, tumors, ulcers, urinary stones, worms, and others. Its use is effortlessly boiling it in 1 liter concentrated into one glass of water, cooling, and consuming it. The content of each recipe consists of seven sticks of *B. medicinalis*, which can be boiled up to three times. The type of application is customized according to the physical condition. For patients who are physically weak, it is recommended to drink 1/3 cup in the morning, 1/3 cup at midday and 1/3 cup in the afternoon (Anam *et al*., 2014; Ardi *et al*., 2019; Herik, 2009; Nurlansi *et al*., 2015).

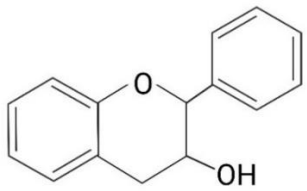
3.3 Phytochemical compounds

Research on the active compounds of plants is essential for drug discovery and development of new treatments to address important diseases due to their biological activity.

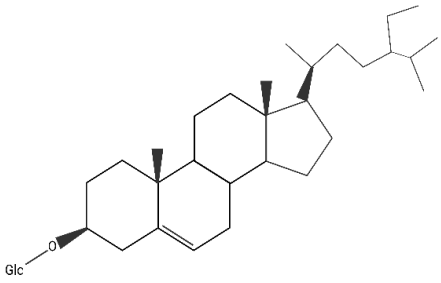
A similar genus of Begonia exhibits a similar class of natural product compounds to those found in *B. medicinalis*. Plants of *Begonia* species contain alkaloid compounds, flavonoid glycosides, pentacyclic triterpenes, tetracyclic triterpenes, tetracyclic triterpenoid glycosides, and steroid glycosides (Zubair *et al*., 2016). Based on phytochemical testing, *B. medicinalis* contains phenolic compounds, flavonoids, alkaloids, saponins, tannins, and polyphenols (Anam *et al*., 2014; Tandi *et al*., 2020). The compound 2-O-β-glucopyranosil cucurbitacin D (Figure 2a is present in the ethyl acetate fraction of *Begonia sp.* based on the isolation and structure elucidation of terpenoid glycoside compounds (Zubair *et al*., 2020). Ultraviolet-Visible spectroscopy results using methanol as the solvent show that the *B. medicinalis* fraction isolate exhibits similar spectra to flavonoid compounds, with peak 1 spectral peak at 275 nm and peak 2 spectral peaks at 225 nm. The flavonoid compounds in the *B. medicinalis* fraction exhibited similarities with flavan-3-ol (Figure 2b) or flavanol absorption peaks based on these wavelengths (Ritna *et al*., 2016). Other research using mass spectroscopy revealed that the ethyl acetate fraction yielded the discovery of two new steroid glycosides, namely β-sitosterol-3-O-β-D-glucopyranoside (Figure 2c) and 9(11)α,16(17)α-dioxirane-20,25-dihydroxy-β-sitosterol-3-O-β-glucopyranoside (Figure 2d) (Zubair *et al*., 2019).



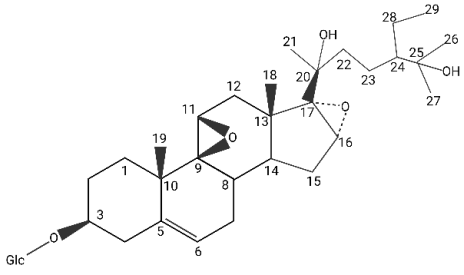
a. 2-O-β-glucopyranosil cucurbitacin D



b. Flavan-3-ol



c. β-sitosterol-3-O-β-D-glucopyranoside



d. 9(11)α,16(17)α-dioxirane-20,25-dihydroxy-β-sitosterol-3-O-β-glucopyranoside

Figure 2. Chemical structures of *B. medicinalis* (figure was reconstructed by BioRender)

3.4 Pharmacology

Several pharmacological actions of *B. medicinalis* have been reported in various studies, both *in vivo* and *in vitro*. There are 11 researchs articles that have reported its pharmacological activities including anticancer, antiviral, antioxidant, immunomodulator, and antidiabetic. In addition, *in vivo* acute toxicity experiments were conducted to evaluate the safety of B. medicinalis. Table 1 summarizes some investigations into the pharmacological activities of *B. medicinalis*.

Table 1. Pharmacological actvities of *B. medicinalis*

Pharmacological activity	Model/cell lines	Samples	Activity/mechanism(s) of action	Reference
Immunomodulatory effect	*Staphylococcus aureus*-infected mice and rats	*B. medicinalis* ethanol extract	Activates macrophage phagocytosis and increases TNF-α and IFN-α cytokine production	(Zubair, *et al*., 2022a)
	Staphylococcus aureus-infected rats	Combination ethanol extract of *B. medicinalis* and *M. oleifera*	Activates macrophage phagocytic activity and increases IFN-γ/TNF-α cytokine levels	(Zubair, *et al*., 2022b)
	Lymphocytes from Mice	N-hexane fraction, ethyl acetate fraction, methanol extract, and water fraction of *B. medicinalis*	Increased lymphocyte cell proliferation	(Khumaidi *et al*., 2020)
	Drosophila melanogaster	Dried *B. medicinalis* ethanolic extract	Modulate the expression of Drs (Toll pathway), Dpt (Imd pathway), and TotA in *D. melanogaster* (JAK-STAT pathway)	(Syamsidi *et al*., 2023)
Anticancer	HeLa and T47D cells	*Begonia sp.* methanol extract	Growth inhibitory on HeLa cells and T47D cells.	(Anam *et al*., 2014)
	MCF-7 and HCT-116 cells	2-o-β-glucopyranosil cucurbitacin D isolated from the ethyl acetate fraction of *Begonia sp.*	Induced apoptosis in MCF-7 and HCT-116 cells	(Zubair *et al*., 2020)
	Hela, MDA-MB, and HT-29 cells	*B. medicinalis* leaf and stem extracts	Potential to treat cancer	(Prihardina & Fatmawati, 2021)
	Artemia salina	Methanol extract, n-hexane fraction,	Inhibit the growth of *A. salina*	(Nurlansi *et al*., 2015)

Pharmacological activity	Model/cell lines	Samples	Activity/mechanism(s) of action	Reference
		ethyl acetate fraction, and water fraction of *B. medicinalis*		
Antiviral and Antioxidant activity	HIV-1-infected MT-4 cells DPPH radical scavenging assay	N-hexane fraction, ethyl acetate fraction, and water fraction of *B. medicinalis*	Inhibits the cytopathic effect of the virus and inhibited free radical reactions	(Zubair *et al*., 2021)
Antidiabetic	Streptozotocin-induced rats	Ethanol extract of *B. medicinalis* leaves	Lowers blood creatinine levels but does not effect on urea levels	(Alaydrus, 2020)
	Streptozotocin-induced rats	Ethanol extract of *B. medicinalis* leaves	Reduces blood glucose levels	(Tandi *et al*., 2020)

3.5 Immunomodulatory activity

The immunomodulatory activity of *B. medicinalis* ethanol extract in male Wistar rats revealed that increasing the dose to 240 mg/kg BW increased macrophage phagocytic activity and TNF- and IFN- cytokine expression. The immunostimulatory activity was attributed to an ethanol extract of *B. medicinalis* that contained high concentrations of total saponins, total phenols, and total flavonoids (Zubair, *et al*., 2022a). Saponins interact with Antigen-presenting cells (APCs) to increase the production of immunostimulants such as interleukins and interferon. Saponins promote T-lymphocyte proliferation, IL-1, IL-2, IL-12, IFN-γ, and TNF-α expression, while inhibiting macrophage phagocytic activity (Bhardwaj *et al.*, 2014; Francis *et al*., 2002; Setiawan & Nugraha, 2016). Phenolic compounds can act as antioxidants, preventing free radical formation and thus developing oxidation reactions. Monocytes exposed to antioxidant compounds can keep their cell shape, allowing them to carry out their phagocytic function actively. Phenolic compounds have also been shown to activate T cells and boost NK cell killing capacity (Kilani-Jaziri *et al*., 2017; Pancawari Ariami *et al.*, 2021). Flavonoids have been shown to increase IL-2 production and lymphocyte proliferation, influencing CD4+ cells and activating Th1 cells (Figure 3). Th1 cell activation influences macrophage-activating factors as well. Flavonoids also stimulate the production of TNF and IFN by NK cells (Martínez *et al*., 2019; Sholikhah & Rahayuningsih, 2015). The immunomodulatory activity of a combination of *B. medicinalis* and *M. oleifera* extracts was also investigated. The combination of extracts

100:100 mg/kg BW has immunomodulatory activity based on macrophage phagocytosis activity and IFN- and TNF- levels (Zubair, *et al*., 2022b). *B. medicinalis* extracts in methanol, n-hexane, ethyl acetate, and aqueous fraction showed increased lymphocyte cell proliferation (immunostimulant), but none inhibited lymphocyte cell proliferation. The highest stimulation index was found in extracts and fractions with a concentration of 100 g/ml (Khumaidi *et al*., 2020). Using gene expression in the Toll, Imd, and JAK-STAT pathways, researchers investigated the immunomodulatory effects of dried *B. medicinalis* extract (DBME) in the *Drosophila melanogaster* model. The survival and locomotor phenotypes of *D. melanogaster* were examined to see if changes in gene expression could be detected at the phenotypic level. DBME was found to induce humoral immune responses in *D. melanogaster* without causing significant phenotypic trade-offs (Syamsidi *et al*., 2023).

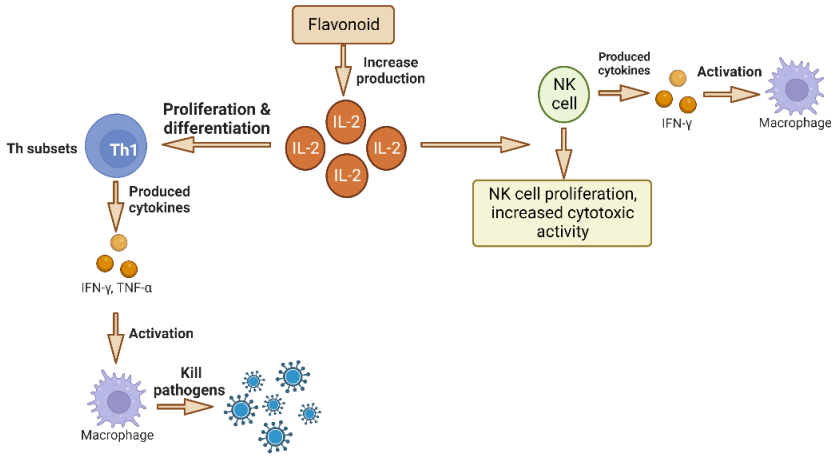


Figure 3. Mechanism of flavonoid action as an immunostimulant (created by BioRender)

3.6 Cytotoxic and anti-cancer activity

The extract of *B. medicinalis* has been confirmed to inhibit the growth of *A. salina* (Nurlansi *et al*., 2015). Furthermore, its methanol extract inhibited the growth of HeLa cells more than T47D cells in the anticancer activity assay. Analysis of the extract's chemical compounds using thin-layer chromatography (TLC) showed that the polyphenol-flavonoid group was involved in the anticancer effect (Anam *et al*., 2014). By controlling the activity of the enzymes that produce reactive oxygen species (ROS), triggering apoptosis, and contributing to cell cycle arrest, flavonoids have been demonstrated to inhibit the proliferation and invasion

of cancer cells. Under normal circumstances, flavonoids has a function as antioxidants in ROS equilibrium, but in cancer cells, flavonoids are potent pro-oxidants that upregulate pro-inflammatory signaling pathways and activate apoptotic pathways (Kopustinskiene *et al*., 2020; Slika *et al*., 2022). Moreover, The cytotoxic activity of *B. medicinalis* against human colorectal colon cancer (HCT-116) and human breast adenocarcinoma (MCF-7) suggested that 2-O-β-glucopyranosyl cucurbitacin D possess cytotoxic effects via inducing apoptosis cells (Zubair *et al*., 2020). Using the MTT assay, the anticancer activity of *B. medicinalis* extracts from leaves and stems was investigated in three different cell lines, including Hela, MDA-MB, and HT-29. The leaf extract had higher total flavonoid content (TFC) than the stem extract. This finding suggest that there is potential to treat cancer with both extracts (Prihardina & Fatmawati, 2021).

3.7 Antiviral and antioxidant activity

Antioxidant and antiviral activity tests revealed that all fractions had potential activity. The *B. medicinalis* n-hexane fraction exhibited the highest antiviral activity in HIV-infected MT-4 cells. Based on GC-MS analysis, the n-hexane fraction contained phenolic compounds (8.38%) and the primary compound carboxylic acid derivative with a percentage area of 76.4%, which are believed to be the primary bioactive chemicals in charge of the antioxidant and antiviral effects. The aqueous fraction (10.05%) had a higher content of terpenoids than the other fractions (Zubair *et al*., 2021).

3.8 Antidiabetic activity

In streptozotocin-induced rats, ethanolic extract of begonia leaves (*Begonia sp.*) at a dose of 50 mg/kg BW effectively reduced blood glucose levels (101.8±20.7 mg/dL). Histopathological studies of the pancreas revealed that *B. medicinalis* extract had no effect on regenerating pancreatic beta cells. This is also because, in general, injured organs are very difficult to restore to normal function, and natural substances have a weak and slow pharmacological impact, requiring a relatively lengthy period to have an effect when compared to artificial medications. The results of histological examination of organs using *B. medicinalis* extract are nearly identical to the results of the drug glibenclamide (the differences are not statistically significant). This is due to the fact that the medicine glibenclamide has a mechanism

of action that stimulates insulin secretion, therefore, it can only lower blood glucose levels but cannot repair pancreatic beta cells (Tandi *et al*., 2020). Even though it did not impacting the urea levels on rat, it also decreased the blood creatinine level at a dose of 100 mg/kg BW, even though it did not affecting the urea levels on rat (Alaydrus, 2020).

3.9 Toxicity study

The toxicity study of *B. medicinalis* is still limited. Only one paper described its acute toxicity profile. The ethanolic extract of *B. medicinalis* was administered to female Wistar rats at various dose levels. At the highest dose, toxicity symptoms were observed, including increased grooming and decreased motor activity. Meanwhile, the LD_{50} of an ethanol extract of *B. medicinalis* herb was 1600 mg/200 g BW, which is classified as mild toxicity by the Indonesia Food and Drug Administration (BPOM) test preparation classification criteria (Putra, 2020).

4. Conclusions

B. medicinalis has long been used as a test treatment for a variety of diseases. Flavanols, 2-O-β-glucopyranosyl cucurbitacin D,β-sitosterol-3-O-β-D-glucopyranoside, and 9(11)α,16(17)α-dioxirane-20,25-dihydroxy-β-sitosterol-3-O-β-glucopyranoside are among the compounds found in the plant. Through various studies that have been conducted, it has been shown that this plant has immunomodulatory, cytotoxic, antiviral, and antioxidant activity, as well as the ability to lower blood sugar and creatinine levels. *In vitro* toxicity tests revealed that this plant is toxic and thus has anticancer potential. The *in vivo* toxicity test revealed that this plant has mild toxicity. However, research into this plant is still in its early stages. More specific research on the content of certain chemical compounds contained in this plant is required to determine which compound causes the pharmacological activity. It is critical to conduct research on the pharmacological activities of unknown plants in order to develop herbal medicinal preparations that can be used to treat diseases all over the world.

Acknowledgements

Author acknowledge The Institute for Research and Community Service, Tadulako University, for the Domestic Cooperation Grant in 2023 (No. 1462.a/UN28.2/PL/2023) and the Magister of Pharmacy, Universitas Islam Indonesia, for the support in this paper.

References

Affandi, O., & Batubara, R. (2019). Study of Medicinal Plant Used By The Ethnic Community of Karo Around Lau Debuk-Debuk Tourism Park, Indonesia. *IOP Conference Series: Earth and Environmental Science*, 374(2019), 1-8. https://doi.org/10.1088/1755-1315/374/1/012055

Alaydrus, S. (2020). Uji Efek Etanol Daun Benalu Batu Terhadap Kreatinin Ureum Tikus Putih Jantan Diinduksi Streptozotocin. *SCIENTIA : Jurnal Farmasi Dan Kesehatan*, 10(1), 33-39.

Anam, S., Yuliet, Ritna, A., Dwimurti, F., Rismayanti, D., & Zubair, M. S. (2014). Cytotoxic Activity of Benalu Batu (*Begonia* sp.) Methanolic Extract: An Ethnomedicine of Wana Tribe Central Sulawesi. *Jurnal Ilmu Kefarmasian Indonesia*, 12(1), 10–16. http://jifi.farmasi.univpancasila.ac.id/index.php/jifi/article/view/176

Ardi, W. H., Zubair, M. S., Ramadanil, & Thomas, D. C. (2019). *Begonia Medicinalis* (*Begoniaceae*), A New Species From Sulawesi, Indonesia. *Phytotaxa*, 423(1), 41–45. https://doi.org/10.11646/phytotaxa.423.1.5

Bhardwaj, J., Chaudhary, N., Seo, H. J., Kim, M. Y., Shin, T. S., & Kim, J. D. (2014). Immunomodulatory Effect of Tea Saponin In Immune T-cells and T-lymphoma Cells Via Regulation of Th1, Th2 Immune Response and MAPK/ERK2 Signaling Pathway. *Immunopharmacology and Immunotoxicology*, 36(3), 202–210. https://doi.org/10.3109/08923973.2014.909849

Francis, G., Kerem, Z., Makkar, H. P. S., & Becker, K. (2002). The Biological Action Of Saponins In Animal Systems: A Review. *British Journal of Nutrition*, 88(6), 587–605. https://doi.org/10.1079/bjn2002725

Herik, N. (2009). Sistem Pengetahuan dan Pemanfaatan Benalu Batu *(Polohi wasu)* Pada Masyarakat Desa Wawopada Kecamatan Lembo Kabupaten Morowali. *Skripsi*. Fakultas Ilmu Sosial Dan Ilmu Politik, Universitas Tadulako.

Khumaidi, A., Widodo, A., Nugrahani, A. W., Sasmito, E., & Fakhrudin, N. (2020). Profil Proliferasi Sel Limfosit Benalu Batu (*Begonia medicinalis*) Asal Kabupaten Morowali Utara Provinsi Sulawesi Tengah. *Jurnal Ilmu Kefarmasian Indonesia*, 18(1), 61–67.

Kilani-Jaziri, S., Mokdad-Bzeouich, I., Krifa, M., Nasr, N., Ghedira, K., & Chekir-Ghedira, L. (2017). Immunomodulatory and Cellular Anti-Oxidant Activities of Caffeic, Ferulic, and P-Coumaric Phenolic Acids: A Structure–Activity Relationship Study. *Drug and Chemical Toxicology*, 40(4), 416–424. https://doi.org/10.1080/01480545.2016.1252919

Kopustinskiene, D. M., Jakstas, V., Savickas, A., & Bernatoniene, J. (2020). Flavonoids As Anticancer Agents. *Nutrients*, 12(2), 1–25. https://doi.org/10.3390/nu12020457

Martínez, G., Mijares, M. R., & De Sanctis, J. B. (2019). Effects of Flavonoids and Its Derivatives on Immune Cell Responses. *Recent Patents on Inflammation & Allergy Drug Discovery*, 13(2), 84–104. https://doi.org/10.2174/1872213x13666190426164124

Moonlight, P.W., Ardi, W.H., Padilla, L.A., Chung, K., Fuller, D., Girmansyah, D., Hollands, R., Jara-Muñoz, A., Kiew, R., Leong, W., Liu, Y., Mahardika, A., Marasinghe, L.D.K., O'Connor, M., Peng, C., Pérez, Á.J., Phutthai, T., Pullan, M., Rajbhandary, S., Reynel, C., Rubite, R.R., Sang, J., Scherberich, D., Shui, Y., Tebbitt, M.C., Thomas, D.C., Wilson, H.P., Zaini, N.H. and Hughes, M. (2018). Dividing and Conquering The Fastest-Growing Genus: Towards A Natural Sectional Classification of The Mega-Diverse Genus Begonia (*Begoniaceae*). *Taxon*, 67(2), 267–323. https://doi.org/10.12705/672.3

Nurlansi, Nasruddin, & Sari, F. (2015). Uji Toksisitas Senyawa Bioaktif Tumbuhan Polohi Wasu (*Begonia* sp.) Terhadap Larva Udang (*Artemia salina Leach*). *Jurnal Sains Dan Kesehatan*,

1(3), 138–145.

Pancawari Ariami, Addien Faqih Pajenengan, & Maruni Wiwin Diarti, W. (2021). Imunostimulator Ekstrak Etanol Anredera Cordifolia Terhadap Titer Widal *Salmonella typhi* O Pada *Rattus Norvergicus* Galur Wistar. *Poltekita : Jurnal Ilmu Kesehatan*, 15(1), 12–18. https://doi.org/10.33860/jik.v15i1.413

Prihardina, B., & Fatmawati, S. (2021). Cytotoxicity of *Begonia medicinalis* Aqueous Extract In Three Cancer Cell Line. *IOP Conference Series: Earth and Environmental Science*, 913(1). https://doi.org/10.1088/1755-1315/913/1/012084

Putra, D. R. (2020). Uji Toksisitas Akut (LD50) Ekstrak Etanol Daun Benalu Batu *(Begonia medicinalis)* Terhadap Tikus Putih *(Rattus norvegicus L.)*. *Skripsi*. Universitas Tadulako.

Ritna, A., Anam, S., & Khumaidi, A. (2016). Identifikasi Senyawa Flavonoid Pada Fraksi Etil Asetat Benalu Batu (*Begonia* sp.) Asal Kabupaten Morowali Utara. *Jurnal Farmasi Galenika (Galenika Journal of Pharmacy) (e-Journal)*, 2(2), 83–89. https://doi.org/10.22487/j24428744.2016.v2.i2.5957

Setiawan, H., & Nugraha, J. (2016). Analisis Kadar IFN-γ dan IL-10 pada PBMC Penderita Tuberkulosis Aktif, Laten dan Orang Sehat, Setelah di Stimulasi dengan Antigen ESAT-6. *Jurnal Biosains Pascasarjana*, 18(1), 50–66.

Sholikhah, A. R., & Rahayuningsih, H. M. (2015). Pengaruh Ekstrak Lompong (*Colocasia esculenta L. Schoot*) 30 Menit Pengukusan Terhadap Aktivitas Fago Sitosis Dan Kadar No (Nitrit Oksida) Mencit *Balb/C* Sebelum Dan Sesudah Terinfeksi Listeria Monocytogenes. *Journal of Nutrition College*, 4(4), 463–468. https://doi.org/10.14710/jnc.v4i4.10148

Slika, H., Mansour, H., Wehbe, N., Nasser, S. A., Iratni, R., Nasrallah, G., Shaito, A., Ghaddar, T., Kobeissy, F., & Eid, A. H. (2022). Therapeutic Potential of Flavonoids In Cancer: ROS-Mediated Mechanisms. *Biomedicine and Pharmacotherapy*, 146(2022), 1-18. https://doi.org/10.1016/j.biopha.2021.112442

Syamsidi, A., Rosa, R.A., Sulastri, E., Rahmah, N., Kamri, R.A., Rumata, N.R., Emran, T. Bin, Sharma, R., Rabaan, A.A., Nainu, F., Zubair, M.S. (2023). Immunomodulatory Effect of *Begonia Medicinalis* Ethanolic Extract in Drosophila*. Biointerface Research in Applied Chemistry,* 13, 1–9. https://doi.org/10.33263/BRIAC136.558

Tandi, J., Paerunan, D. E., Kenta, Y. S., Mulyani, S., Studi, P., Kimia, P., & Tadulako, U. (2020). Uji Potensi Ekstrak Daun Benalu Batu (*Begonia* sp) Terhadap Kadar Glukosa Dalam Darah Dan Gambaran Histopatologi Pankreas Tikus Putih Jantan (*Rattus norvegicus*). *Jurnal Ilmiah Manuntung*, 6(2), 286–298.

Zubair, M. S., Alarif, W. M., Ghandourah, M. A., & Anam, S. (2019). A New Steroid Glycoside From *Begonia* sp.: Cytotoxic Activity and Docking Studies. *Natural Product Research*, 35(13), 1–8. https://doi.org/10.1080/14786419.2019.1669026

Zubair, M. S., Alarif, W. M., Ghandourah, M. A., Anam, S., & Jantan, I. (2020). Cytotoxic Activity of 2-o-β-Glucopyranosil Cucurbitacin D From Benalu Batu (*Begonia* sp.) Growing in Morowali, Central Sulawesi. *Indonesian Journal of Chemistry*, 20(4), 766–772. https://doi.org/10.22146/ijc.43626

Zubair, M. S., Anam, S., Khumaidi, A., Susanto, Y., Hidayat, M., & Ridhay, A. (2016). Molecular Docking Approach To Identify Potential Anticancer Compounds From Begonia (*Begonia* sp). *AIP Conference Proceedings*, 1755(July 2016). https://doi.org/10.1063/1.4958513

Zubair, M. S., Khairunisa, S. Q., Sulastri, E., Ihwan, Widodo, A., Nasronudin, & Pitopang, R. (2021). Antioxidant and Antiviral Potency of *Begonia medicinalis* Fractions. *Journal of Basic and Clinical Physiology and Pharmacology*, 32(4), 845–851.

https://doi.org/https://doi.org/10.1515/jbcpp-2020-0476

Zubair, M. S., Syamsidi, A., Ihwan, Sulastri, E., Idris, Rahman, A., Widyasari, N., Sanjaya, I. P., & Pakaya, D. (2022a). Immunomodulatory Activity of *Begonia medicinalis* Ethanolic Extract in Experimental Animals. *Indonesian Journal of Pharmacy*, 33(4), 1–8.

Zubair, M. S., Syamsidi, A., Sulastri, E., Pakaya, D., Asita, N., Tanriono, L. V., & Poluan, J. C. (2022b). Immunomodulatory Effects of Combined Ethanolic Extracts of *Begonia medicinalis* and *Moringa oleifera* in Wistar Rats Infected with Staphylococcus aureus. *Malaysian Journal of Chemistry*, 24(4), 144–149.