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FULL PAPER

Toxic effects of bintaro (cerbera manghas) seed extract on aedes *aegypti* mosquito

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The use of chemicals in disease vector control has had a negative impact on the quality of environmental health. To reduce this impact, this study aimed to evaluate the effect of different bintaro fruit seed extracts (n-hexane and 96% ethanol) on the mortality of Ae. *aegypti* mosquitoes. A total of 1120 samples of 3-5-day-old adult Ae. aegypti mosquitoes were used in this study, with 3 repetitions. The research design was experimental, using a post-test-only controlled group design. Mosquito mortality was recorded after 24 hours of observation, while the toxicity effect of the spray on adult mosquitoes was recorded at 3-minute intervals for 20 minutes. The results showed that the administration of n-hexane and 96% ethanol extract solutions of C. manghas fruit seeds with different concentrations had different impacts on mosquito mortality. LC50 and LC90 for the n-hexane solution were 11,840 (118,400 ppm) and 26,646 (262,460 ppm), while the 96% ethanol extract solution was 5,207 (52,070 ppm) and 10,436 (104,360 ppm) in 100 mL of distilled water. An ANOVA test on n-hexane and 96% ethanol extracts of C. manghas seeds showed a significant difference between the two types of solutions. The yield of the maceration method using 96% ethanol solvent showed higher results than the n-hexane yield, with a significant value of 0.001 ($p < 0.05$). There is a significant difference between each concentration of bintaro fruit seed extract and the mortality of *Ae. aegypti* mosquitoes.

KEYWORDS

Aedes *aegypti*; toxicity; extract; cerbera manghas; biolarvicide.

Introduction

Dengue fever, chikungunya, and the Zika virus are just a few of the mosquito-borne illnesses that pose a significant threat to public health around the world. Controlling the population of the Aedes aegypti mosquito, which is the principal vector for these diseases and is one of the most important factors in reducing the frequency of these diseases, is essential. The use of chemicals in mosquito vector control such as larvicides is an important element to minimize disease transmission. Organochlorines, organophosphates, carbamates, and pyrethroids are types of synthetic insecticides that have been used for decades in vector control programs. Although the use of synthetic insecticides dramatically reduces the risk of vector-borne diseases, overuse, and misuse of conventional chemicals has led to mosquito resistance. Efforts to use biopesticides are encouraged as a promising future economic and environmentally friendly strategy to overcome the problem of mosquito vector resistance [1-3]. This method of controlling the Aedes aegypti mosquito with biolarvicides, which can be found naturally or made in a lab, has shown some promise as a way to handle the mosquito population [4-7].

It is possible to get biolarvicides from the seeds of the bintaro fruit, which is also known as Cerbera manghas. These chemicals could be used to get rid of Aedes aegypti mosquito infestations. The fruit of the bintaro tree is widespread throughout Southeast Asia, and the seeds of this tree have a long history of usage in traditional medicine. Extracts from the seeds of the bintaro fruit have been demonstrated in recent research to have larvicidal effects on the Aedes aegypti mosquito, which is a vector for disease [8-11].

The efficiency of bintaro fruit seed extracts as a biolarvicide for the control of the Aedes aegypti mosquito was the subject of one research project that was carried out in Indonesia. Within this study, a laboratory bioassay was used to find out how well the extracts killed the eggs. According to the findings, the extracts exhibited a substantial larvicidal effect on the Aedes aegypti mosquito larvae, as demonstrated by a mortality rate of up to one hundred percent at a concentration of one thousand parts per million (ppm) [12]. More research was done in Thailand. They looked at the chemicals that were in extracts from the fruit seeds of the Bintaro tree and how well they killed Aedes aegypti mosquito larvae. The research found that the extracts contained a number of chemicals, one of which was a cardiac glycoside called cerberin. These compounds were responsible for the larvicidal effect. The research also discovered that the extracts had a substantial larvicidal effect on the larvae of the Aedes aegypti mosquito, with a mortality rate of up to 90 percent at a concentration of 100 parts per million (ppm) [13].

Results from these studies show that extracts from the fruit seeds of the Bintaro tree might be useful as a biolarvicide to get rid of the Aedes aegypti mosquito. However, further research is required to examine the efficacy of these extracts under field settings and to determine the influence they have on organisms that are not their intended targets. When it comes to the control of mosquito populations, the use of biolarvicides has various advantages over the use of standard insecticides. They pose less of a threat to people, animals, and the environment, and they reduce the likelihood that mosquitoes may become resistant to the treatment. It is also possible for biolarvicides to be more focused against certain kinds of mosquitoes, hence limiting the impact on organisms that are not the intended targets [14,15].

Finally, chemicals found in the fruit seeds of the bintaro tree show a lot of promise for being used as a biolarvicide to kill the Aedes aegypti mosquito, which is a major vector of diseases. There needs to be more research done to see how well these extracts work in the wild and to find out what effects they have on organisms that are not their intended targets. The use of biolarvicides shows promise as a method for decreasing mosquito populations and lowering the number of cases of diseases that are transmitted by mosquitoes.

According to the study, Bintaro (Cerbera manghas) seed extract is effective as a biological larvicide on Aedes aegypti instar III larvae [16]. A similar study in 2022 also showed the effectiveness of Bintaro leaf extract against instar III larvae of Aedes aegypti mosquitoes. This study used 5 types of doses with 5 replicates [17]. For an in-depth study of the potential of bintaro fruit extract as a bioinsecticide material, this study aims to evaluate the effect of bintaro fruit seed extract on the mortality of Ae. aegypti mosquitoes using n-hexane and 96% ethanol of bintaro fruit seeds (C. manghas).

Method

This study used the post-test only controlled group design with 2 controls. The extract solutions used were n-hexane and 96% ethanol of bintaro (Cerbera manghas) fruit seeds at 6 levels (0.325%, 0.65.5%, 1.25%, 2.5%, 5%, and 10%). Preliminary tests were conducted with 6 treatments and 2 controls in 3 replications. As for the advanced test with 12 treatments and 2 controls in 3 replications, the subjects used in this study were adult female or male Ae. Aegypti mosquitoes that were alive and actively moving aged 3-5 days obtained from the laboratory of the Centre for Vector and Reservoir Disease Research and Development in Salatiga. To study how to kill insects, n-hexane and ethanol solution extracts of bintaro (C. manghas) fruit seeds (Figure 1) were sprayed on mosquitoes. The samples were kept in a dark place to be protected from sunlight for 3 x 24 hours while occasionally stirring. After that, it was filtered to get the filtrate and the residue. The residue was mixed with the same solvents (n-hexane and 96% ethanol) repeatedly until the liquid became clear. This meant that the extraction process was completed at its best. The filtrate was collected and evaporated using a rotary evaporator until a thick extract was obtained.

Research flow

The equipment used in this study includes a room thermometer, hygrometer, glass chamber measuring 70x70x70 cm^3, aspirator, pipette, stopwatch, and measuring cup. In addition, a mini compressor sprayer with a particle size of 0.3MM was also used. The materials used were n-hexane and 96% ethanol solution extracts of bintaro (*C. manghas*) fruit seeds with concentrations of 0.325%, 0.65%, 1.25%, 2.5%, 5%, and 10%, sterile distilled water, and live and actively moving adult Ae. Aegypti mosquitoes.

In this study, 20 Ae. Aegypti mosquitoes were released in a glass chamber and observed for 20 minutes. The n-hexane and 96% ethanol extract solutions of bintaro (*C. manghas*) seeds were sprayed at predetermined concentrations 9 times using a sprayer. Mosquitoes that fainted or died were recorded at each predetermined time period. Mosquitoes were then transferred into paper cups using an aspirator and kept in paper cup holding for 24 hours. The number of dead mosquitoes was counted after 24 hours.

FIGURE 1a C manghas tree

FIGURE 1b C manghas

TABLE 1 Toxicity test results of n-hexane and ethanol extracts of C. manghas fruit seeds observed after 24 hours

Sample Test	Concentrate (%)	Number of Dead Mosquitoes				Mortalitas		LC_{50}	LC_{90}
		I	II	III	Total	Rerata	%		
n-hexane extract C. manghas fruit seeds	0.32	11	4	8	23	7,67	38,33		
	0.65	2	7	8	17	5.67	28.33		
	1.25	2	8	2	12	4.00	20.00	11.840	26.646
	2.5	6	1	11	18	6.00	30.00		
	5	3	11	5	19	6.33	31.67		
	10	4	9	10	23	7.67	38.33		
	Control (-)	0	0	0	0	0	0		
Ethanol Extract of C. manghas Fruit Seeds	0.32	5	7	9	21	7.00	35.00		
	0.65	8	8	10	26	8.67	43.33		
	1.25	10	11	8	29	9.67	48.67		
	2.5	11	11	9	31	10.33	51.67	5.207	10.436
	5	9	18	15	42	14.00	70.00		
	10	17	16	12	45	15.00	75.00		
Control (-)	Kontrol (-)	0	0	0	0	0	0		

*Total number of mosquitoes in 1 treatment was 20 with control distilled water solution

Results

According to standardized testing conducted by the World Health Organization (WHO) [16], the mortality of the test mosquitoes from the effect of insecticides was determined by the mortality rate with 24 hours post-contact observation on the insecticide sprayed wall. The toxicity test showed that the administration of n-hexane and ethanol extracts caused the highest mortality rate in the test animals, which amounted to 63.33%, followed by n-hexane extract at 38.33% (Table 1).

In this study, the extraction of bintaro fruit seeds using 96% ethanol solvent showed a higher mortality rate of test mosquitoes compared to n-Hexane solvent. This is related to the polar nature of bintaro fruit seed oil, so that bintaro fruit seed oil tends to dissolve into solvents that are polar as well. Tests of n-hexane and ethanol extracts with 3 repetitions showed differences between the two types of solutions. The average toxicity of Ae. Aegypti mosquitoes in each repetition of ethanol extract was more than 50% at concentrations of 2.5%, 5%, and 10%, while the control was not found in each repetition (Figure 2).

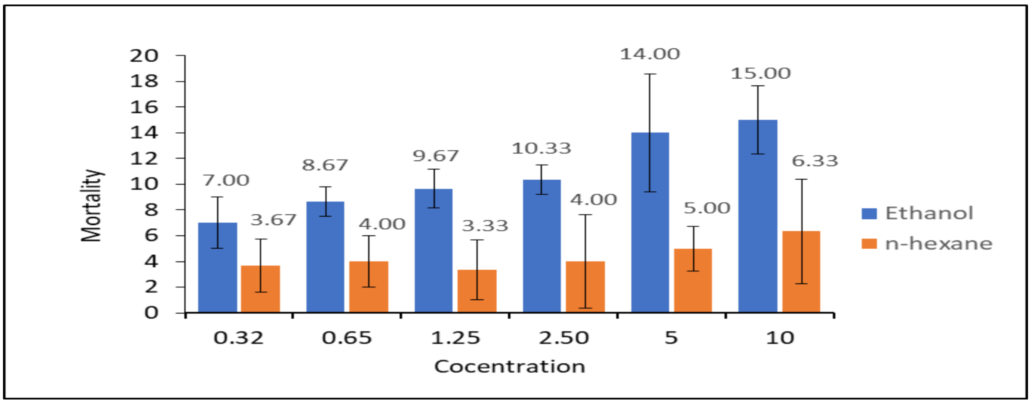

FIGURE 2 Mosquito mortality to n-hexane and ethanol extracts of C. manghas fruit seeds

An increase in the concentration of ethanol extract of C. manghas fruit seeds was followed by an increase in the mean mosquito toxicity score, while this did not occur with n-hexane. This is due to the polar nature of the ethanol solvent which easily attracts active compounds contained in the sample, such as saponins, alkaloids, and tannins which are toxic to the zoological system. Secondary metabolites of flavonoids, tannins, alkaloids, terpenoids, and saponins were found in the ethanol extract of *C. manghas*. The application of n-hexane and ethanol extract solutions of *C. manghas* fruit seeds with different concentrations had different impacts on mosquito mortality. The results of probit analysis of LC_{50} and LC_{90} of both *C. manghas* seed solutions showed that mortality could reach 50% and 90% at certain concentrations of extract solutions on Ae. Aegypti mosquitoes. For LC_{50} and LC_{90} of n-hexane solution, the concentrations were 11,840 (118,400 ppm) and 26,646 (262,460 ppm), respectively, while for ethanol extract solution, the concentrations were 5,207 (52,070 ppm) and 10,436 (104,360 ppm), respectively. Measurements were taken in 100 ml of distilled water at a time 24 hours after treatment. The results of room measurements at the time of the experiment showed an average temperature of 28 °C with an average humidity of 79%. ANOVA test results on n-hexane and ethanol extracts of C. manghas seeds showed a significant difference between the two types of solutions. The yield of the maceration method using 96% ethanol solvent showed results where 96% ethanol maceration was higher than the yield of n-hexane.

Discussion

Natural ingredients have biological activities that can affect insect behaviour, such as inhibition of nesting activity, feeding inhibition, and feeding refusal. In addition, natural ingredients can also affect insect physiological activities, such as growth inhibition, ovicidal, larvicidal, and mortality. Humidity and temperature are very important in mosquito survival. At each phase of mosquito growth, temperature affects the dynamism of the Ae. Aegypti population. Adult mosquitoes can live in temperatures between 11 °C and 35 °C. Mosquito activity will decrease at 11 °C and if it exceeds 35 °C, mosquitoes will live shorter lives. The optimal humidity required for mosquito growth is between 60% and 80%. In this study, the temperature and humidity were in optimum conditions that support mosquito survival. Mosquito mortality occurs due to insecticide exposure to mosquitoes. The increase in the concentration of n-hexane and ethanol extracts was directly proportional to the increase in mosquito mortality from 1 to 24 hours of observation. The content of secondary metabolite compounds contained in the ethanol solution extract ofintaro fruit seeds is greater, thus causing an increase in mosquito mortality during the 24-hour observation. The n-hexane and 96% ethanol solution extracts of bintaro fruit seeds have different levels of insecticidal activity. The ethanol extract was more potent in killing mosquitoes than the n-hexane extract. The difference in ability in insecticidal activity is caused by different concentrations of metabolic compounds. According to Kuddus *et al.* (2011) [17], bintaro fruit contains steroids, while ripe and fresh bintaro fruit seeds contain cerberin alkaloids, a substance that tastes bitter and toxic. Alkaloid compounds that have a function as anti-fungal were found in bintaro bark by Singh *et al. (*2012) [18]. In addition, alkaloids, tannins, and saponins are also found in bintaro, which has antibacterial, cytotoxic, and central nervous system depressant properties due to the presence of two substances alkaloids and saponins [19]. The way alkaloid compounds work is by inhibiting the activity of the enzyme acetylcholinesterase which affects the transmission of nerve impulses, causing the enzyme to phosphorylate and become inactive. This results in the inhibition of the acetylcholine degradation process resulting in the accumulation of acetylcholine in the synapse gap. This leads to impaired transmission which results in decreased muscle coordination, convulsions, respiratory failure, and death [19].

Menurut Gaillard *et al.* (2004)[20] and Chang *et al.* (2000)[21], cerberin is a monoacetyl neriifolin compound. Bintaro fruit seeds contain six new types of cardenolid glycosides, namely 3β-O-(2'-O-acetyl-α-L-thevetosyl)-14β-hydroxy-7-en-5β-card 20(22)-enolide, (7,8-dehydrocereberin), 17β-neriifolin, deacetyltahnginin, tangh-inin, cerebrin, and 2'-O-acetyl-cerleaside. Of these six compounds, cerberin has potential cardiotoxicity [22]. Cerberin also has toxic properties that can cause anorexia in larvae. [23,24].

Flavonoids have antimicrobial, antifungal, and cytotoxic effects on larvae [25,26]. Saponins are detergent-like substances and have the ability to damage cell membranes [27]. Tannin components have the property of blocking insects from digesting food because tannins can bind to proteins in the digestive system that are needed by insects for growth, so that the process of protein absorption is disrupted. Tannins can also suppress feed consumption, growth rate, and insect survivability [28]. Individuals who experience tannin poisoning have clinical symptoms such as anorexia, depression, and the presence of ulcers in the digestive tract, depending on how much tannin enters the individual's body [29].

Conclusion

The toxicity levels of n-hexane and ethanol extracts of bintaro fruit seeds against Aedes aegypti mosquitoes are not the same. The ethanol toxicity is higher than N-hexane. The higher the concentration of ethanol extract of bintaro (Serbera manghas) seeds, the higher the morality rate of Aedes aegypti mosquitoes. Bintaro fruit seeds have potential as a bioinsecticide material for the control of Aedes aegypti mosquitoes. Bintaro fruit seed extract is promising as a bioinsecticide to control Aedes aegypti mosquitoes, which are the main vectors of mosquito-borne diseases. Further research is needed to evaluate the effectiveness of these extracts under field conditions and to assess their impact on non-target organisms. Biolaricides offer a promising approach to controlling mosquito populations and reducing the incidence of mosquito-borne diseases.

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Conflict of interest

No conflicts of interest are disclosed by the writers.

Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

All of the authors contributed to the study's concept and layout. The authors handled the material preparation, data gathering, and analysis and wrote the first draft of the manuscript, while all other authors provided feedback on earlier revisions. All authors read and approved the final manuscript.

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References

[1] (a) A. Badolo, E. Ilboudo-Sanogo, A.P. Ouédraogo, and C. Costantini, Evaluation of the sensitivity of Aedes aegypti and Anopheles gambiae complex mosquitoes to two insect repellents: DEET and KBR 3023, *Trop. Med. Int. Heal.*, **2004**, *9*, 330–334. [Crossref], [Google Scholar], [Publisher] (b) H. Ayoub, M. Khairy, F.A. Rashwan, H.F. Abdel-Hafez, Synthesis of calcium silicate hydrate from chicken eggshells and combined joint effect with nervous system insecticides, *Asian J. Green Chem.*, **2022**, *6*, 103-111. [Crossref], [Google Scholar], [Publisher] (c) M.B. Abdulsalam, A.T. Numan, Synthesis, characterization, and biological activity of mixed ligand complexes from 8-hydroxyquinoline and new ligand for *β*-enaminone, *Chem. Methodol.*, **2022**, *6*, 962-976. [Crossref], [Google Scholar], [Publisher]

[2] (a) M.V. Yu, A.B. Abdulcarim, M.I.N. Baligod, F.S.E. Dela Cruz, C.J.V. Ordoñez, A. Garcia-Bertuso, Bioefficacy of the Ethanolic Crude Extract of the Wild Leek, Allium ampeloprasum L. (Amaryllidaceae), Against the Third and Fourth Larval Stages of Aedes aegypti L. (Culicidae), *Acta Trop.*, **2023**, 107067. [Crossref], [Google Scholar], [Publisher] (b) M. Khalil, S. Noor, Z. Ahmad, F. Ahmad, Fate of Pakistani exported mango due to its toxicity (Heavy metals, pesticides, and other toxic organic components), *J. Appl. Organomet. Chem.*, **2023**, *3*, 86-107. [Crossref], [Google Scholar], [Publisher] (c) S. Ismail, Botanical insecticides and mineral oils synergize toxicity of imidacloprid against Bemisia tabaci (Hemiptera: Aleyrodidae). *Prog. Chem. Biochem. Res.*, **2021**, *4*, 295-304. [Crossref], [Publisher]

[3] (a) K. Karunamoorthi, S. Sabesan, Insecticide resistance in insect vectors of disease with special reference to mosquitoes: a potential threat to global public health, *Heal. Scope*, **2013**. [Google Scholar], [Publisher] (b) B. Fazeli-Nasab, L. Shahraki-Mojahed, Z. Beigomi, M. Beigomi, A. Pahlavan, Rapid detection methods of pesticides residues in vegetable foods, *Chem. Methodol.*, **2022**, *6*, 24-40. [Crossref], [Google Scholar], [Publisher] (c) F. Ahmad, M. Mehmood, A critical review of photocatalytic degradation of organophosphorus pesticide "Parathion" by different mixed metal oxides, *Adv. J. Chem. A* , **2022**, *5*, 287-310. [Crossref], [Publisher]

[4] J.I. Arredondo-Jiménez, K. M. Valdez-Delgado, Aedes aegypti pupal/demographic surveys in southern Mexico: consistency and practicality, *Ann. Trop. Med. Parasitol*, **2006**, *100*, 17–32. [Crossref], [Google Scholar], [Publisher]

[5] A. Kroeger, *A. Lenhart, M. Ochoa, E. Villegas, M. Levy, N. Alexander, P. McCall,* Effective control of dengue vectors with curtains and water container covers treated with insecticide in Mexico and Venezuela: cluster randomised trials, *Bmj*, **2006**, *332*, 1247–1252. [Crossref], [Google Scholar], [Publisher]

[6] K.A. Polson, W.G. Brogdon, S.C. Rawlins, D.D. Chadee, Characterization of insecticide resistance in Trinidadian strains of Aedes aegypti mosquitoes, *Acta Trop*, **2011**, *117*, 31–38. [Crossref], [Google Scholar], [Publisher]

[7] J.Whitehorn, S. Yacoub, K.L. Anders, L.R. Macareo, M.C. Cassetti, V.C. Nguyen Van, P.Y. Shi, B. Wills, C.P. Simmons, Dengue therapeutics, chemoprophylaxis, and allied tools: state of the art and future directions, *PLoS Negl. Trop. Dis*, **2014**, *8*, 3025. [Crossref], [Google Scholar], [Publisher]

[8] M. Saxena, E.B. Jadhav, M.S. Sankhla, M. Singhal, K. Parihar, K.K. Awasthi, G. Awasthi, Bintaro (Cerbera odollam and Cerbera manghas): an overview of its eco-friendly use,

pharmacology, and toxicology, *Environ. Sci. Pollut. Res.*, **2023**, *30*, 71970-71983. [Crossref], [Google Scholar], [Publisher]

[9] A. Aziz, R. Sahknan, K. Khayan, S. Wradoyo, Comparative biochemical effects of seeds extract Cerbera manghas and leaves Carica papaya the vector of Aedes aegypti mosquitos, *J. Entomol. Res.*, **2021**, *45*, 453–460. [Crossref], [Google Scholar], [Publisher]

[10] A. R. W. Elbers , R. Meiswinkel, Culicoides (Diptera: Ceratopogonidae) and livestock in the Netherlands: comparing host preference and attack rates on a Shetland pony, a dairy cow, and a sheep, *J. Vector Ecol.*, **2015**, *40*, 308–317 [Crossref], [Google Scholar], [Publisher]

[11] D. Meisyara, D. Tarmadi, A. Zulfitri, A. Fajar, M. Ismayati, S.K. Himmi, T. Kartika, I. Guswenrivo, S. Yusuf, November. Larvicidal Activity of Bintaro (Cerbera odollam) against Culex quinquefasciatus. In *IOP Conference Series: Earth and Environmental Science*, **2020**, *591*, 012010. [Crossref], [Google Scholar], [Publisher]

[12] A. Betancourt , J. R. Loaiza, An effective sampling tool for adult crabhole inhabiting Deinocerites mosquitoes, *J. Vector Ecol.*, **2016**, *41*, 200–203. [Crossref], [Google Scholar], [Publisher]

[13] K.J. Gellatly, S. Krim, D.J. Palenchar, K. Shepherd, K.S. Yoon, C.J. Rhodes, S.H. Leeand Marshall, J. Clark, Expansion of the knockdown resistance frequency map for human head lice (Phthiraptera: Pediculidae) in the United States using quantitative sequencing, *J. Med. Entomol.*, **2016**, *53*, 653-659. [Crossref], [Google Scholar], [Publisher]

[14] M. Osanloo, M. M. Sedaghat, A. Sanei-Dehkordi, A. Amani, Plant-derived essential oils; their larvicidal properties and potential application for control of mosquito-borne diseases, *Galen Medical Journal*, **2019**, *8*, 1532. [Crossref], [Google Scholar], [Publisher]

[15] R. Waliwitiya, C.J. Kennedy, C.A. Lowenberger, Larvicidal and oviposition-altering activity of monoterpenoids, trans-anithole and rosemary oil to the yellow fever mosquito Aedes aegypti (Diptera: Culicidae), *Pest Management Science: formerly Pesticide Science*, **2009**, *65*, 241–248. [Crossref], [Google Scholar], [Publisher]

[16] W. H. Organization, Guidelines for testing mosquito adulticides for indoor residual spraying and treatment of mosquito nets, World Health Organization, **2006.** [Google Scholar], [Publisher]

[17] M.R. Kuddus, F. Rumi, M.M. Masud, C.M. Hasan, Phytochemical screening and antioxidant activity studies of Cerbera odollam Gaertn, *International Journal of Pharma and Bio Sciences*, **2011**, *2*, 413–418. [Google Scholar], [Publisher]

[18] H. Singh, G. Alsamarai, M. Syarhabil, Performance of botanical pesticides to control post-harvest fungi in citrus, *Int. j. sci. eng. res.*, **2012**, *3*, 1–4. [Google Scholar], [Publisher]

[19] L.F. Olusola, J. Baba, I.L. Muhammad, Medicinal plants for the treatment of malaria and typhoid diseases, *J. Med. Plants Res.*, **2023**, *17*, 16–27. [Crossref], [Google Scholar], [Publisher]

[20] Y. Gaillard, A. Krishnamoorthy, F. Bevalot, Cerbera odollam: a 'suicide tree'and cause of death in the state of Kerala, India, *J. Ethnopharmacol.*,**2004**, *95*, 123–126. [Crossref], [Google Scholar], [Publisher]

[21] L.C. Chang, J.J. Gills, K.P. Bhat, L. Luyengi, N.R. Farnsworth, J.M. Pezzuto, A.D. Kinghorn, Activity-guided isolation of constituents of Cerbera manghas with antiproliferative and antiestrogenic activities, *Bioorganic Med. Chem. Lett.*, **2000**, *10* , 2431-2434. [Crossref], [Google Scholar], [Publisher]

[22] S. Cheenpracha, C. Karalai, C. Ponglimanont, K. Chantrapromma, New cytotoxic cardenolide glycoside from the seeds of Cerbera manghas, *Chem. Pharm. Bull.*, **2004**, *52*, 1023–1025. [Crossref], [Google Scholar], [Publisher]

[23] N.E.A. Murray, M.B. Quam, A. Wilder-Smith, Epidemiology of dengue: past, present and future prospects, *Clin. Epidemiol.*, **2013**, 299–309. [Crossref], [Google Scholar], [Publisher]

[24] I.M. Arisanti, D. Dono, Bioaktivitas campuran ekstrak biji Barringtonia asiatica L.(Kurz.)(Lecythidaceae) dan getah Azadirachta indica A. Juss.(Meliaceae) terhadap larva Spodoptera litura F.(Lepidoptera: Noctuidae), *Agrikultura*, **2015**, 26. [Crossref], [Google Scholar], [Publisher]

[25] A. Samanta, G. Das, S. K. Das, R Roles of flavonoids in plants, *Carbon*, **2011**, *100*, 12–35. [Google Scholar], [Publisher]

[26] O.M. Andersen, K.R. Markham, *Flavonoids: chemistry, biochemistry and applications. CRC press,* **2005.** [Google Scholar], [Publisher]

[27] F. Mert-Türk, Saponins versus plant fungal pathogens. *J. Cell Mol. Biol*., **2006**, *5*, 13–17. [Google Scholar], [Publisher]

[28] E.A. Yunita, N.H. Suprapti, J.W. Hidayat, Pengaruh ekstrak daun teklan (Eupatorium riparium) terhadap mortalitas dan perkembangan larva Aedes aegypti, *Bioma*, **2009**, *11*, 11–17. [Google Scholar], [Publisher]

[29] P. Frutos, G. Hervas, F.J. Giráldez, A.R. Mantecón, Tannins and ruminant nutrition, *Spanish J. Agric. Res.*, **2004**, *2*, 191–202. [Crossref], [Google Scholar], [Publisher]

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