Malaysian Applied Biology (2024) 53(6): 123-129
https://doi.org/10.55230/mabjournal.v53i6.16

Research

Preliminary Exploration of Bioactive Compounds and Anthelmintic Activity in *Diospyros kaki* Fruits

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ABSTRACT

Helminths, or parasitic worms, pose a significant global health concern, affecting more than 25% of the world's population. In Malaysia, these infections are endemic, with varying prevalence rates among different populations, especially those impacting economically disadvantaged communities. The present study aimed to determine the secondary metabolites present and evaluate the anthelmintic activity of *Diospyros kaki* fruit extracts against earthworms. Hexane, ethyl acetate, ethanol, and water extracts of *Diospyros kaki* fruits were obtained via the cold maceration technique. Preliminary phytoconstituent screening of *Diospyros kaki* fruit extracts was performed to identify the phytoconstituents present in the extracts. The anthelminthic activities of different extracts (200 and 300 mg/mL) of *Diospyros kaki* fruits were evaluated separately in adult Malaysian earthworms (*Pheretima posthuma*). The durations of paralysis and death of individual worms were determined and compared with those of the standard drug albendazole at a concentration of 40 mg/mL. Ethyl acetate extract of *D. kaki* fruits at a concentration of 300 mg/mL resulted in better anthelmintic activity than the standard drug, albendazole, and other *D. kaki* fruit extracts. Qualitative phytochemical analysis revealed the presence of tannins, flavonoids, alkaloids, and volatile oils that might contribute to the anthelmintic activity of *D. kaki* fruits. Further research is intended to isolate anthelmintic bioactive compounds that could serve as new lead structures for developing alternative novel herbal anthelmintic agents.

Key words: Anthelminthic, *Diospyros kaki* fruits, extracts, *Pheretima posthuma*, qualitative chemical tests

Article History
Accepted: 6 December 2024
First version online: 25 December 2024

Cite This Article:
Kalusalingam, A., Johari Rozario, A.H., Subramanian, P., Khan, A., Rajapandi, S., Pandian, S.M.K., Thanikachalam, P.V., Ming, L.C. & Ikmal, A.M. 2024. Preliminary exploration of bioactive compounds and anthelmintic activity in *Diospyros kaki* fruits. Malaysian Applied Biology, 53(6): 123-129. https://doi.org/10.55230/mabjournal.v53i6.16

INTRODUCTION

Helminths, or worms, are a diverse group of invertebrate animals that harbor various pathogens capable of impacting human health (Motran *et al*., 2018). These parasitic worms affect more than 25% of the global population, leading to significant illness and disability (Jourdan *et al*., 2018). According to the PAHO/WHO, approximately 1.5 billion people worldwide suffer from infections caused by soil-transmitted helminths, establishing it as the most widespread infection across the globe (PAHO/WHO, Pan American Health Organization, 2024). The key species impacting humans encompass roundworms (*Ascaris lumbricoides*), whipworms (*Trichuris trichiura*), and hookworms (*Necator americanus* & *Ancylostoma duodenale*) (Torgerson *et al*., 2015). Proper warmth and ample moisture are pivotal for the successful hatching or embryonic development of soil-transmitted helminth (STH) eggs in the environment, as well as the maturation of larvae. Factors such as poverty, inadequate sanitation, and substandard hygiene practices—such as the absence of handwashing with soap after defecation and before meals, along with walking barefoot—constitute substantial contextual elements contributing to human infections. In these socioecological contexts, various types of STH infections are frequently observed. The transmission of STHs occurs through exposure to contaminated soil, such as hookworms, or the consumption of foods contaminated with eggs, such as *A. lumbricoides* and *T. trichiura* (Anuar *et al*., 2014).

Anthelmintics refer to medications employed for the management and regulation of infections caused by parasitic nematodes, trematodes, and cestodes in both animals and humans (Nixon *et al*., 2020). Benzimidazoles (e.g., mebendazole, albendazole, fenbendazole & flubendazole), imidazothiazoles (levamisole), macrocyclic lactones (ivermectin and moxidectin), and the amino-acetonitrile derivative monepantel are the four major classes of common anthelmintics used to treat nematode infections in livestock. On the other hand, chemotherapy remains the mainstay for controlling all helminthiases (Zajíčková *et al*., 2020). Anthelmintic resistance has been reported in all classes of anthelmintics (Fissiha & Kinde, 2021).

Medicinal plants, whether in their entirety or specific components such as roots, stem bark, leaves, fruits, peels, or seeds, are utilized for medicinal and therapeutic purposes because of the presence of bioactive compounds (Sarker *et al*., 2023). Research has revealed that secondary metabolites, including condensed tannins, flavonoids, and hydrolyzed tannins, are specific polyphenol classes that have undergone extensive scrutiny for their anthelmintic properties. Numerous in vitro and in vivo studies have substantiated these effects against a diverse array of parasitic and free-living nematodes (Spiegler *et al*., 2017).

Traditional medicines, including anthelmintic substances, present significant potential as reservoirs of potent treatments (Romero-Benavides *et al*., 2017). Owing to resistance occurring in all classes of anthelmintics, the use of medicinal plants that possess anthelmintic activities is being considered. Members of the Diospyros genus are part of the Ebenaceae family and are frequently grown in temperate regions worldwide, such as China, Korea, Japan, Brazil, Turkey, and Italy (Matheus *et al*., 2022). Among the approximately 350 species in the Diospyros genus, *Diospyros kaki*, known for producing edible fruits, which are commonly known as persimmon fruits, stands out in commercial fruit cultivation. This recognition is attributed mainly to the nutritional and functional excellence of the fruits of *Diospyros kaki.* The plant is known by various names across languages. In Chinese, it is "Shi" or "Shi zi"; in French, "Kaki" or "Plaqueminier"; in German, "Kaki" or "Kakibaum"; and in Italian, "Cachi." Tamil speakers call it "Japan Pazham," whereas in Japanese, it is "Kaki" or "Kakinoki." The Korean name is "Gam," and in Malay, it is "Buah kaki" or "Kesemek." The Portuguese call it "Caqui," the Russians "Kaki" or "Khurma," and the Spanish "Caqui" or "Kaki del Japon." In Thailand, it is known as the "Phlap chin" (Ferreira da Vinha *et al*., 2021).

Diospyros kaki has been reported to have therapeutic effects, such as antioxidant, antiaging, antihypertensive, antiatherosclerosis, anticoagulant, antiosteoporotic, anti-inflammatory, antiallergenic, antidiabetic, anti-anaphylactic, antibacterial, anticancer, antitumor, immunologic, hemostatic and tyrosinase inhibitory effects. In Malaysia, people have traditionally used *D. kaki* fruits to cure helminthic infections in children (Ojha *et al*., 2023). Hence, this study aimed to investigate the presence of phytoconstituents and the anthelmintic properties of selected plant fruits to scientifically validate the anthelmintic potential of *D. kaki* fruits. The anthelmintic activity of *D. kaki* fruits against the earthworm, *Pheretima posthuma* has not been studied. Hence, the present study aimed to investigate the presence of phytoconstituents and the anthelmintic properties of selected plant fruits to scientifically validate the anthelmintic potential of *D. kaki* fruits.

MATERIAL AND METHODS

Plant material

Diospyros kaki fruits were purchased from Nilai, Negeri Sembilan, in February 2024. The *D. kaki* fruits were identified and authenticated by Dr. Shamsul Bin Khamis, botanist, University Kebangsaan Malaysia, Bangi, Malaysia (Specimen voucher: ID108/2024) (Figure 1).

Preparation of Extracts

The fruits of *D. kaki* were cleaned by rinsing with water. The fruits were then sliced into small pieces. The fruits were coarsely ground and equally divided into four portions and macerated separately with distilled water, ethanol, ethyl acetate, and hexane by cold maceration method for 7 days. The extract was filtered via a filter cloth and concentrated via a rotary vacuum evaporator at 60°C. The efficiency of the extraction of the concentrated extracts was determined on a dry-weight basis (Ibrahim *et al*., 2023). The color, consistency, and percentage yield of the fruit extracts are tabulated in Table 1. The fruit extracts were stored at 4°C in a refrigerator until subsequent analysis.

Fig. 1. *Diospyros kaki* fruits (Butt *et al*., 2015)

Phytoconstituent analysis

Preliminary phytochemical screening of *D. kaki* fruit extracts was qualitatively carried out to identify phytoconstituents such as carbohydrates by Benedict's test, glycosides by Borntranger's test, alkaloids by Dragendroff's test, volatile oils by Sudan III test, flavonoids by Shinoda test, tannins by Lead acetate test and saponins by Froth test present in the extracts per the standard textual procedure (Kancherla *et al*., 2019). The results are summarized in Table 2.

Anthelmintic activity

Extracts at concentrations of 200 mg/mL and 300 mg/mL were used to assess the anthelmintic effect by observing the time of paralysis and death of the earthworms (Das *et al*., 2021). Albendazole at a concentration of 40 mg/mL was used as a standard, and distilled water was used as a control. In total, 10 groups, each comprising one earthworm, were introduced to 10 mL of the respective formulations. Group 1, which served as the control, consisted of 10 mL of distilled water. Group 2 served as the standard drug albendazole at a concentration of 40 mg/mL. Groups 3 and 4 received distilled water extract of *D. kaki* fruits at concentrations of 200 and 300 mg/mL, respectively. Groups 5 and 6 were treated with ethanol extracts at concentrations of 200 and 300 mg/mL, respectively. Groups 7-8 were treated with ethyl acetate at concentrations of 200 and 300 mg/mL, respectively. Groups 9 and 10 were treated with hexane extracts at concentrations of 200 and 300 mg/mL, respectively. The time taken for individual worms to experience paralysis and eventual death was observed and recorded to assess the anthelmintic potency. Paralysis was determined when no movement was observed in the worms even after being transferred to distilled water, and death was concluded when the worms lost their motility completely by either failing to respond even after being touched with the needle, followed by fading of their body color. The test was repeated three times to ensure the reliability of the results obtained, to ensure their validity, and to obtain accurate data regarding the results (Sharma *et al*., 2016). All the data are presented as the means ± SDs and are tabulated in Table No. 3.

Statistical analysis

Statistical analysis was carried out via independent samples t-tests via SPSS software. Each extract was compared with the standard drug, albendazole, and the significant differences between the groups (*p* values) were calculated at 0.01 and 0.001 (Kancherla *et al*., 2019).

RESULTS

The color, consistency, and percentage yield of *Diospyros kaki* fruit extracts are tabulated in Table 1. The color of the concentrated distilled water extracts, ethanol extracts, and hexane extracts was dark brown with a semisolid consistency. However, the concentrated ethyl acetate extracts were light brown with a semisolid consistency. The percentage yield of concentrated extracts of *D. kaki* fruits was 18.58% for distilled water, followed by 15.26% for hexane, 15.07% for ethanol, and 10.45% for ethyl acetate.

The preliminary phytoconstituent screening revealed that all four extracts (distilled water, ethanol, ethyl acetate, and hexane) were positive for carbohydrates, glycosides, proteins, alkaloids, volatile oils, and terpenoids, flavonoids, and tannins. For saponins, only the distilled water and hexane extracts had positive results.

Table 1. Color, consistency, and % yield of *D. kaki* fruit extracts

S. No	Extract of *D. kaki* fruits	Color	Consistency	% yield
1	Distilled water	Dark brown	Semi-solid	18.58
2	Ethanol	Dark brown	Semi-solid	15.07
3	Ethyl Acetate	Light brown	Semi-solid	10.45
4	Hexane	Dark brown	Semi-solid	15.26

Table 2. Preliminary phytoconstituent test of *D. kaki* fruit extracts

S. No.	Constituents	Extracts			
		Distilled water	Ethanol	Ethyl acetate	Hexane
1.	Carbohydrates	+	+	+	+
2.	Glycosides	+	+	+	+
4.	Proteins	+	+	+	+
5.	Alkaloids	+	+	+	+
6.	Volatile oils	+	+	+	+
7.	Flavonoids	+	+	+	+
8.	Tannins	+	+	+	+
9.	Saponins	+	-	-	+

+ indicates presence; - indicates absence

In the present study, *D. kaki* fruit extracts were assessed to demonstrate their anthelmintic efficacy in paralyzing and killing earthworms and compared their efficacy to albendazole, a standard anthelmintic drug, and the results are presented in Table 3.

Table 3. Anthelmintic activity of *D. kaki* fruit extracts

Group	Treatment	Concentration (mg/mL)	Time taken to paralyze (min) Mean ± SD	Time taken for death (min) Mean ± SD
1	Distilled water	-	-	-
2	Albendazole	40	24.6 ± 0.36	31.2 ± 0.57
3	Distilled water extract	200	9.8 ± 2.36***	11.3 ± 2.84***
4		300	6.5 ± 0.5***	7.0 ± 0.5***
5	Ethanol extract	200	51.3 ± 1.04*	53.5 ± 1.5*
6		300	18.2 ± 0.28**	16.8 ± 0.28**
7	Ethyl Acetate extract	200	8.8 ± 1.27***	4.4 ± 1.8***
8		300	2.0 ± 0.0***	2.5 ± 0.0***
9	Hexane extract	200	91.8 ± 1.04*	94.3 ± 1.04*
10		300	61.0 ± 1.0*	63.5 ± 1.32*

The values are expressed as the means ± SDs; n=3; - represents no effect.
***p<0.001 - Highly significant **p<0.01 - Significant, and *p>0.05 - less significant

Albendazole at a concentration of 40 mg/mL caused paralysis in 24.6 min and death in 31.2 min. All the extracts showed concentration dependent anthelmintic activity against the worms selected. Among the extracts of *D. kaki* fruits evaluated, the ethyl acetate extract exhibited the most potent anthelmintic activity followed by distilled water extract. The ethanol extract showed moderate anthelmintic activity whereas hexane extract showed mild anthelmintic activity. At both concentrations of 300 mg/mL, ethyl extract caused paralysis and death significantly (p<0.001) in 2.0 min and 2.5 min, respectively to the worms. The distilled water extract at the concentration of 300 mg/mL showed high significant (p<0.001) anthelmintic activity with paralysis occurring in 6.5 min and death in 7.0 min. The ethanol extract demonstrated significant (p<0.01) anthelmintic activity at the concentration of 300 mg/mL with paralysis at 18.2 min and death at 16.8 min respectively, while at a concentration of 200 mg/mL, it exhibited less significant (p<0.05) anthelmintic effect with paralysis at 51.3 min and death at 53.5 min respectively. In contrast, the hexane extract was the least effective and produced paralysis at 91.8 min and 61.0 min followed by death at 94.3 min and 63.5 min at the concentration of 200 mg/mL and 300 mg/mL respectively. These findings suggest that the ethyl acetate extract, especially at higher concentrations, could be a promising natural alternative to conventional anthelmintic drugs like albendazole.

DISCUSSION

The medicinal plant under study is claimed to have numerous therapeutic activities including anthelmintic efficacy. In this present study, various extracts of *D. kaki* fruits were prepared by a cold maceration method using different solvents ranging from polar to non-polar and investigated their anthelmintic potency against the worms, *P. posthuma*. The polarity of a solvent may affect the percentage yield obtained from the crude drug. Different solvents have different extraction abilities, which are dependent on both the polarity of the extraction medium and the different types of solvents used (Ibrahim *et al*., 2023). The polarity of solvents increases, with hexane being nonpolar, followed by ethyl acetate, ethanol, and distilled water having the highest polarity (Nawaz *et al*., 2020). No drying process was applied before extraction to preserve the phytochemicals in the fruits of *D. kaki* because drying of plant materials before extraction may not always be better, as certain active pharmacological compounds may be lost during this process (Oikeh *et al*., 2020). The percentage yield was the highest for the distilled water extracts of *D. kaki* fruits, followed by the hexane extract, ethanol extract, and ethyl acetate extract, with percentages of 18.58%, 15.26%, 15.07%, and 10.45%, respectively. Phytochemicals found in *D. kaki* fruits during the preliminary phytoconstituent screening (Table 2) may be responsible for the evaluated anthelmintic activity (Table 3) and may be optimistically considered a substitutive approach to control helminth infections.

The earthworm, *P. posthuma* has traditionally been used as a model for preliminary anthelmintic activity due to their anatomical and physiological similarities to intestinal worms, human parasites, and ease of availability. Earthworms have a slimy mucilaginous layer made up of complex polysaccharides that allow them to move freely. When the mucopolysaccharide membrane is damaged, irritation causes restricted movement and paralysis, resulting in the worm's death (Lahare *et al*., 2021). Anthelmintics refer to medications employed for the management and regulation of infections caused by parasitic nematodes, trematodes, and cestodes in both animals and humans (Nixon *et al*., 2020). Albendazole is a common anthelmintic medication used to treat nematode infections in livestock, hence, that is why it is being used as a standard drug in this experiment (Zajíčková *et al*., 2020).

The ethyl acetate extract of *D. kaki* showed the highest anthelmintic efficacy against the tested worms, *P. posthuma*, followed by the distilled water extract. The ethanol extract showed moderate activity, while the hexane extract was the least effective. Extracts of *D. kaki* presented concentration-dependent anthelmintic properties that might be due to the presence of tannins, alkaloids, volatile oils, and flavonoids. The ethyl acetate extract presented the most effective anthelmintic activity than distilled water extract at a concentration of 300 mg/mL Hence, it may be considered a potent anthelmintic agent despite not possessing saponins. Hence, it may be suggested that the presence of saponins in distilled water extract might not contribute to anthelmintic activity. This is supported by an earlier study to test anthelmintic activity in the bark of *Zizyphus joazeiro* which possessed abundant triterpenoids saponin derivatives such as jujubosides, and joazeirosides that did not exhibit the anthelmintic activity (Gomes *et al*., 2016).

This present study is supported by an earlier report conducted on *L. madayiparanse* on *P. posthuma* using an in-vitro method where the findings suggested that the observed anthelmintic activity might be due to the tannins present in it. The anthelmintic activity of medicinal plants is due to the binding of tannins to free proteins in the gastrointestinal tract of host animals or glycoprotein on the cuticle of the parasite, leading to death (Chiranjeevi *et al*., 2018). A study found that *Ruta chalepensis* volatile oil caused 87.5% *H. contortus* worm mortality at 1 mg/mL. *R. officinalis* demonstrated antiparasitic and antileishmanial activity against *Leishmania major* promastigote (IC50 = 0.08 µL/mL) (Aouadi *et al*., 2021). Another study suggested that volatile oils from *Eucalyptus staigeriana* could reduce worm eggs and larval development, as well as combat nematodes in sheep's digestive tracts (Ramdani *et al*., 2023).

Another study on *Tagetes erecta* against *P. posthuma* using the in-vitro method suggested that the presence of alkaloids, tannins, and flavonoids is responsible for anthelmintic activity. This is because alkaloids may have effects on the central nervous system, causing paralysis in the earthworm. The effect would be due to the presence of the steroidal alkaloid, oligoglycosides, which may inhibit the transfer of sucrose from the stomach to the small intestine; thus, in conjunction with its antioxidant effect, it is capable of reducing nitrate generation, which could disrupt local homeostasis, which is required for the development of helminths. Furthermore, tannins can harm the cuticle and hypodermis by binding to a glycoprotein on the cuticle of worms, causing paralysis. Flavonoids are believed to participate in the energy generation process, causing parasites' paralysis and death (Goswami & Singh, 2018).

Hence, the proposed mechanism of action of the ethyl acetate extract involves the disruption of neural function, leading to paralysis, followed by damage to the earthworm cuticle, causing further paralysis. Additionally, interference with energy metabolism reduces ATP production, and the induction of oxidative stress damages cell membranes, ultimately resulting in earthworm death. All extracts of *D. kaki* fruits expressed anthelmintic activity in a concentration-dependent order, with a shortened meantime for paralysis and death at concentrations of 200 mg/mL and 300 mg/mL. This may be due to the higher concentration of phytochemicals present to produce effective anthelmintic activity.

CONCLUSION

The experimental evidence obtained in the present study could provide a rationale for the anthelminthic property of *D. kaki* fruits. The presence of phytoconstituents such as tannins, alkaloids, volatile oils, and flavonoids in *D. kaki* fruits might be responsible for its anthelmintic activity. These findings indicate that the extracts derived from *D. kaki* fruits possess important secondary metabolites that are important for producing anthelmintic activity and might be useful for the treatment of helminthic infections by disrupting the life cycle of worms and preventing their growth. The anthelmintic activity observed in *D. kaki* fruits led to further research to isolate anthelmintic bioactive compounds that could serve as new lead structures for developing alternative novel herbal anthelmintic agents. Investigations of the exact mode of action and safety aspects are necessary to determine the feasibility of developing effective and safe drug preparations for the treatment of helminthic infections.

ACKNOWLEDGEMENT

The authors are thankful to the management, of KPJ Healthcare University, Kota Seriemas, Nilai 71800, Negeri Sembilan, Malaysia, for providing laboratory facilities and support.

ETHICAL STATEMENT

Not applicable

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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