Science World Journal Vol. 20(No 1) 2025 https://dx.doi.org/10.4314/swj.v20i1.45
www.scienceworldjournal.org
ISSN: 1597-6343 (Online), ISSN: 2756-391X (Print)
Published by Faculty of Science, Kaduna State University

Full Length Research Article

ANTIBACTERIAL, ANTICANCER AND ANTIOXIDANT PROPERTIES OF THE STEM AND LEAF EXTRACT OF *DODONAEA VISCOSA*

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ABSTRACT
Dodonaea viscosa is commonly used in traditional medicine because of its purported therapeutic benefits in the treatment of bacterial infections, cancer and inflammation among others. The present study aims to evaluate the antibacterial, antioxidant and anticancer effects of the leaf and stem extracts of *Dodonaea viscosa*. The antibacterial properties of the extracts of *D. viscosa* leaf and stem were evaluated using agar well diffusion method while the anticancer effect was evaluated using MTT (cytotoxicity) assay. The antioxidant potential of the plant was assessed via DPPH (free radical scavenging) assay method. Of all the extracts of the leaf and stem of *D. viscosa* evaluated, the methanol and chloroform extracts of the leaf as well as the hexane extract of the stem produced the highest antibacterial activity. The quantitative phytochemical analysis revealed that the 3 extracts with the highest antibacterial activity contain significant amount of flavonoids and polyphenols. In addition, the 3 extracts had cytotoxic effects on liver and cervical cancer cells, and high antioxidant properties in the DPPH assay. Therefore, this study presents *D. viscosa* as a plant with multiple therapeutic effects justifying its intensive use in traditional and folk medicine.

Keywords: *Dodonaea viscosa,* anticancer, antimicrobial, antioxidant, cytotoxicity.

INTRODUCTION

Since time immemorial, plants have been used as alternative sources of natural compounds for the treatment of many diseases including bacterial infections, inflammation, diabetes and cancer (Hamed *et al*., 2020). The African continent has been ravaged mainly by infectious diseases due to poor sanitary practices. This situation necessitates the need to identify plants with antibacterial effects to combat the scourge of infection, alongside other ailments that have ravaged the region. Among the many plants used for the treatment of bacterial infections in Nigeria, the most populous country in Africa is *Dodonaea viscosa* (Herrera-Calderon *et al*., 2021). The use of the plant is gaining momentum because of its purported medicinal benefits. Generally, plants are choice alternatives to clinical drugs because of lower side effects (Pothiraj *et al*., 2021).

Dodonaea viscosa (L) (Sapindaceae family) is a small tree with rigid twiglike branches (Alavijeh *et al*., 2013). It is a dioecious or monoecious single or multi-stem shrub that is about 7 m high with the ability to survive extreme growing conditions (Lawal and Yunusa, 2013). *D. viscosa* has been reported to contain numerous bioactive compounds that include alkaloids, terpenoids, saponins, tannins, steroids, flavonoids and carbohydrates (Mehmood *et al*., 2023; Aly and Balkhy, 2012). Specifically, the extract of *D. viscosa* has been used for the traditional treatment of rheumatoid arthritis, waist pain, gout, sore throat, diarrhea, tooth aches and typhoid fever (Shanmugavasan and Ramachandran, 2011; Rani and Mohan, 2009). The grinded stem powder of *D. viscosa* facilitates bone healing (Senthilkumar *et al*., 2006). The leaves have been identified to possess glucose lowering activity, hepatoprotective and lipid lowering activity (Ahmad *et al*., 2012; Veerapur *et al*., 2010). Recently, Priya *et al.* (2021) reported the antimicrobial activities of the leaves of the plant against infectious human pathogens. Other studies have also reported the antioxidant and anticancer effects of the extract of *D. viscosa* which has increased the therapeutic uses of the plant in folk medicine (Herrera-Calderon *et al*., 2023; Malik, 2022). It is on this premise that the current study was conducted to evaluate the antibacterial, anticancer and antioxidant properties of the leaf and stem of *D. viscosa*. The study hopes to add more scientific evidence that will support the therapeutic value of the plant.

MATERIALS AND METHODS

Plant Extraction

The leaves and stem bark of *Dodonaea viscosa* were collected in Zaria, Kaduna state, washed with distilled water and dried under shade for 2 weeks. The plant sample was assigned the voucher specimen number, KASU/BCH/9501. The dried samples were pulverized to powder using pestle and mortar. The powdered leaf was soaked successively in n-hexane, chloroform and methanol for 48 hours each at room temperature. The extracts from each solvent were collected separately via filtration with No.1 Whatman filter paper and dried to solid in a rotary evaporator at 40^{o}C. The same procedure was repeated for the ground stem powder to collect the extracts. The dried extracts of the leaf and stem of *D. viscosa* were stored at 4^{o}C for further analysis.

Antibacterial Assay

The agar well diffusion method (Ngamsurach and Praipipat, 2022) was used to evaluate the antibacterial activity of the extracts of *D. viscosa.* Clinical isolates of *Salmonella* Typhi were collected from Microbiology Department of Kaduna State University, and sub-cultured in Mueller-Hinton broth. The isolates were aseptically innoculated into a nutrient broth and incubated at 37°C for 24 hours. A cork borer (6 mm diameter) was used to make four wells each corresponding to the treatment doses. About 0.2 ml of the different doses of extract prepared were added to the corresponding wells.

The plates were left on the bench for about 15 mins for diffusion to begin after which they were incubated at 37°C for 24 hours and the zones of inhibition were recorded in millimitres.

Total flavonoid content (TFC) assay

The total flavonoid content was determined using the modified aluminum chloride assay method described by Sembiring *et al*. (2018). Briefly, 50 µl of extracts (1 mg/ml) or standard quercertin (30, 40, 50, 60, 70, 80, 90, and 100 µg/ml) was added to 10 µl of 10% aluminum chloride solution followed by the addition of 150 µl of ethanol in a 96-well plate. Thereafter, 10 µl of 1 M sodium acetate was finally added to the mixture, using ethanol as the reagent blank. All reagents were mixed and incubated for 40 min at room temperature and protected from light. The absorbance was then measured at 415 nm on a microplate reader (Biorad, USA). Total flavonoid contents were expressed as mg Quercetin Equivalents (QE) per g of plant extract.

Total phenolic content (TPC) assay

The total phenolic assay was performed using the Folin-Ciocalteu method as described by Sembiring *et al*. (2018). Briefly, 25 µl of each extract diluted in ethanol was mixed with 100 µl of Folin–Ciocalteu reagent and shaken for 60 sec in a flat-bottom 96-well microplate. The mixture was left for 4 min and then 75 µl of sodium carbonate solution (100 g/l) was added, and the mixture was vortexed 1 min. After 2 hours of incubation at room temperature, the absorbance was measured at 765 nm using the microplate reader (Biorad, USA). Gallic acid dilutions of between 10 and 200 mg/l were used as standards for calibration. Total phenolic contents were expressed as mg Gallic Acid Equivalents (GAE) per g of plant extract.

Antioxidant Assay

The DPPH radical scavenging assay method was used to evaluate the antioxidant activity of each extract as described by Zahratunnisa *et al*. (2017). About 20 µl of the extract (100, 500, 1000, 1500, 2000 µg/ml) of *D. viscosa* or standard was mixed 180 µl of DPPH solution (0.147 mM) in a 96 well plate. The mixtures were incubated for 30 min at room temperature in the dark, and absorbance was read at 517 nm using a microplate reader (Biorad, USA). Methanol was used as the blank while ascorbic acid was used as the standard. All tests were performed in triplicate. The percentage scavenging ability (%) was calculated as follows:

$$\%\ Inhibition = \frac{Absorbance\ of\ Standard - Absorbance\ of\ Extract}{Absorbance\ of\ Standard}\ x\ 100$$

Concentration of samples resulting in 50% inhibition on DPPH (IC_{50} value) was calculated using dose response curve with GraphPad Prism software.

Anticancer assay

Cell Culture

The HepG2 (liver cancer) and Hela (cervical cancer) cell lines were purchased from American Type Culture Collection (ATCC) and maintained at 37°C in an incubator supplemented with 5% CO_2. The HepG2 and Hela cells were grown separately in Roswell Park Memorial Institute (RPMI)-1640 medium, supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. The cells were incubated in a direct heat humidified CO_2 incubator with 5% CO_2 at 37°C. At 70 to 80% cell culture confluence, sub-culturing was routinely done to maintain the cells.

Cytotoxicity Assay (MTT assay)

The cytotoxicity study was performed using 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) assay as described by Waziri *et al*. (2016). Both HepG2 and Hela cells were seeded separately at a density of 2×10^3 cells per well for 24 hours and treated with either 12.5, 25, 50, 100 and 200 µg/ml of the *D. viscosa* crude extracts for 48 h while 0.1% dimethyl sulfoxide (DMSO) was used as negative control. After 48 hours of treatment, 20 µl of MTT solution (5 mg/ml) was added to each well (final concentration of MTT was 0.5 mg/ml) and the plate was incubated at 37°C for 4 hours. The reaction was terminated by the addition of 150 µl of DMSO to solubilize the MTT-formazan crystals formed by metabolically viable cells. The optical density was measured by absorbance at 570 nm using an xMark microplate spectrophotometer (Biorad, USA). The percentage cytotoxicity was calculated using the formula:

$$\text{Cytotoxicity (\%)} = 1 - \frac{\text{Absorbance of treated } cells}{\text{Absorbance of } control\ cells} \times 100$$

Statistical analysis

The results obtained are presented as mean ± SEM (standard error of mean) of at least three separate experiments. One-way analysis of variance (ANOVA) was applied to determine the statistical significant difference between antibacterial activities of the various extract concentrations using SPSS (ver. 27, IBM, USA).

RESULTS

Antibacterial assay

Table 1 shows the antibacterial activity of *D. viscosa* stem and leaves extracts. The n-hexane, chloroform and methanol extracts of the leaves of *D. viscosa* significantly inhibited the growth of *Salmonella* Typii at all treatment concentrations. For the hexane extract of the leaf, increase in treatment concentration did not have any effect on the zone of inhibition. The lowest treatment concentration (50 mg/ml) for the n-hexane and chloroform extracts of the leaf of *D. viscosa* produced the highest zone of inhibition.
However, only the hexane and methanolic extracts of the stem of *D. viscosa* had effect on the growth of *Salmonella* Typhi and this effect corresponded to the dose of treatment (Table 1). The hexane extract (300 mg/ml) produced the highest zone of inhibition. The chloroform extract of the stem did not produce any zone of inhibition on the growth of *Salmonella* Typhii.

Total flavonoid and polyphenol assay

The total flavonoid content (TFC) and total polyphenol content (TPC) of the most active extracts of *D. viscosa* in antibacterial assay is shown in Table 2. There were no significant differences ($p<0.05$) in the TFC of the extracts of *D. viscosa* leaf. However, the methanol leaf extract (264.1 ± 0.06) had the highest total flavonoid content with the chloroform leaf extract (250.5 ± 0.01) having the least TFC. Similarly, the total phenolic concentrations (TPC) of the extracts of *D. viscosa* revealed a similar pattern with the TFC. The methanolic leaf extract (214.8±1.74) showed the highest total phenolic concentration while the chloroform leaf extract (161.9±0.32) showed the least TPC. The concentrations of the phenolic content of the hexane stem, chloroform and methanol extract of *D. viscosa* leaf differ significantly ($p<0.05$).

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Antioxidant assay

The antioxidant activity of the most active extracts of *D. viscosa* was evaluated via DPPH free radical scavenging assay method as shown in Figure 1. The antioxidant activity was investigated by measuring the inhibitory concentrations of the 3 most active extracts at 50% and all 3 extracts significantly ($p<0.05$) scavenged the free radicals.

Table 1: Antibacterial effects of the extracts of the leaf and stem of *D. viscosa*

Treatment	Diameter Zones of Inhibition				
	300 mg/ml	200 mg/ml	100 mg/ml	50 mg/ml	10% DMSO
Leaf extract					
Hexane	20.0±0.00^a	20.0±1.00^a	20.0±1.00^a	20.0±0.00^a	00.0±0.00^b
Chloroform	13.0±0.00^b	14.5±0.50^b	20.0±1.00^a	22.0±1.00^a	00.0±0.00^c
Methanol	18.0±1.00^b	18.0±0.00^b	15.5±0.50^c	20.0±0.00^a	00.0±0.00^d
Stem extract					
Hexane	23.0±1.00^a	23.0±1.00^a	20.0±1.00^b	20.0±0.00^b	00.0±0.00^c
Chloroform	00.0±0.00^a	00.0±0.00^a	00.0±0.00^a	00.0±0.00^a	00.0±0.00^a
Methanol	20.5±0.50^a	15.5±0.50^b	00.0±0.00^c	00.0±0.00^c	00.0±0.00^c

Values are presented as mean ± Standard error of mean (SEM) of triplicate determinations. Values with different alphabets across the row indicate statistical significance difference ($p<0.05$) at 95% confidence interval. DMSO – Dimethylsulphooxide, mm – millimeters, mg – milligram

Table 2: Total Flavonoid Content (TFC) and Total Polyphenol Content (TPC) of n-hexane stem, chloroform and methanol leaf extracts of *Dodonaea viscosa*

D. viscosa Extracts	TFC (µg/ml) of extract	TPC (µg/ml) of extract
Hexane stem	252.0±0.03^a	183.8±1.29^b
Chloroform leaves	250.5±0.01^a	161.9±0.32^a
Methanol leaves	264.1±0.06^a	214.8±1.74^c

Result is presented as mean ± SEM of triplicate determination. Values with different alphabets within the column indicate statistical significance difference ($p<0.05$) at 95% confidence interval. IC_{50} – inhibitory concentration at 50%, µg – microgram, ml – milliliter.

Anticancer assay (Cytotoxicity assay)

Table 3 reveals the anticancer effect of the 3 extracts with the highest antibacterial activity. The cytotoxicity effects of the extracts was evaluated using MTT assay and all 3 extracts significantly ($p<0.05$) exerted cytotoxic effects on the cancer cell lines. From the result, the n-hexane stem extract exerted the highest anticancer activity (17.6±1.18 µg/ml) on the liver cancer cell line and this was followed by the methanol leaf extract (20.2±0.08 µg/ml), and then the chloroform leaf extracts (25.8±0.41). However, the methanol leaf extract (12.8±1.58 µg/ml) showed the highest anticancer activity on the cervical cancer cell line, followed by the n-hexane stem extract (19.2±1.55 µg/ml) and then chloroform leaf extract (33.8±4.32 µg/ml).

Table 3: Effect of *D. viscosa* extracts on the viability of liver and cervical cancers

D. viscosa Extracts	IC_{50} (µg/mL) of extract against cell line	
	HepG2	Hela
Hexane stem	17.6±1.18	19.2±1.55
Chloroform leaves	25.8±0.41	33.8±4.32
Methanol leaves	20.2±0.08	12.8±1.58

Result is presented as mean ± SEM (standard error of mean) of triplicate determination. Significance value (p-value) ≤0.05 indicate statistical significant difference at 95% confidence interval

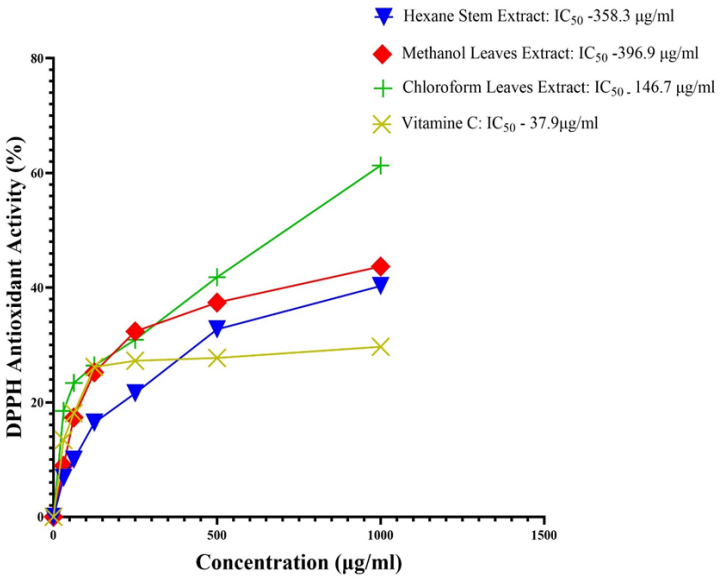

Figure 1: DPPH antioxidant activity (%) of the extracts of *Dodonaea viscosa*

DISCUSSION

Although numerous studies have reported the antibacterial properties of *D. viscosa,* this study compared the antibacterial properties of the non-polar (n-hexane and chloroform) and polar (methanol) extracts of the stem and leaves of the plant as well as the antioxidant and anticancer properties. Of all the leaf extracts of *D. viscosa* evaluated, the chloroform and methanol extracts showed higher antibacterial activity. The zones of inhibition of *Salmonella* Typhii growth produced by the chloroform and methanol extract is significantly ($p<0.05$) higher than those of the other leaf extracts. The evaluation of the different extracts of the stem shows that the hexane extract has the highest antibacterial activity. The zone of inhibition of *Salmonella* growth by the non-polar hexane extract of the stem is significantly ($p<0.05$) higher than that of the chloroform and methanol extracts. This result corresponds with the study by Pérez-Narváez *et al.* (2023) and Malik (2022) that reported strong antibacterial activities of the ethanolic extract of *D. viscosa* leaf. This suggests that the extracts of the leaf and stem could serve as sources of antibacterial agent especially in an era of the rising bacterial infections and antibacterial resistance. The inhibition zone on *Salmonella* Typhi growth could also be a pointer to the potency of the plant in

ameliorating typhoid fever. The ability of the plant extract to inhibit bacterial growth can be attributed to some of the secondary metabolites contained in the stem and leaves. Previous studies have identified some secondary metabolites such as tannins, alkaloids, flavanoids, terpenoids, glycosides, steroids and phenols that are believed to contribute to the therapeutic effects of *D. viscosa* (Priya *et al*., 2021). Some of these secondary metabolites can produce reactive oxygen species within bacterial cells resulting in cellular damage and eventual inhibition of the bacterial growth. Non-polar compounds such as terpenes with antibacterial activity have been reported to be present in hexane extracts of most traditional plants while tannins and flavonoids found in methanolic extracts also serve antibacterial function (Priya *et al*., 2021).

The anticancer assay shows that the extracts with high antibiotic activity equally caused cytotoxic effect on liver (HepG2) and cervical (cervical) cancer cell lines. Liver cancer is one of the most devastating cancers characterized by hepatocellular damage induced by reactive oxygen species and inflammation. Our results revealed that the non-polar hexane stem extracts exerted the highest cytotoxic effect on the liver cancer cell while the polar methanolic leaf extract exerted the highest cytotoxic effect on the cervical cancer cell line. This suggests that both extracts have potential anticancer compounds that contributed the cytotoxic effects observed in this study. This result corresponds with the report of Herrera-Calderon *et al*. (2023) who reported the anticancer activity of *D. viscosa* on colorectal cancer. Malik (2022) also reported the anticancer activity of the methanol and ethyl acetate stem extracts of *D. viscosa*. Previously, it was reported that phytochemicals such as flavonoids, polyphenols and terpenes have strong anticancer properties (Ali *et al*., 2023; Kluska and Woźniak, 2021; Kopustinskiene, 2020). Our results revealed that the methanol leaf and n-hexane stem extract of *D. viscosa* contain significant amounts of flavonoid and polyphenols. Therefore, we postulate that the cytotoxic effect of both the hexane stem and methanol leaf extracts of the plant is likely due to the presence of flavonoids and polyphenols. This reinforces the need to explore bioactivity guided isolation of the bioactive compounds in *D. viscosa* as an avenue to identify specific anticancer agents that could positively aid the development of novel options for cancer treatment considering the high cost of cancer treatment and side effects of conventional chemotherapy.

Most living cells generate reactive oxygen species and free radicals during various metabolic processes that are responsible for different diseases such as cancer, diabetes, and a host of others. Antioxidants generated from inorganic sources such as butylated hydroxytoluene presents side effects of concern hence the need to identify antioxidants of organic sources (Malik, 2022). All 3 most active antibacterial extracts evaluated in this study displayed strong antioxidant activity in the DPPH assay. The DPPH activity from our results also revealed the free radical scavenging ability of the various extracts of the plant. This correspond with the report of Malik (2022) who noted the highest scavenging activity of the extracts of the flower of *D. viscosa* and a high scavenging potential by the root and stem of the plant. These scavenging activities could be due to the TPC and TFC present in the various extracts of *D. viscosa.* Phenolic and flavonoid compounds have been identified for their unique ability to mop of free radicals, lower oxidative stress and improve antioxidant capacity at cellular level (Rodríguez-Arce and Saldías, 2021). This result further corroborate the reports on the antioxidant potential of the extracts of *D. viscosa* and this will aid better management of diseases associated with cancer and oxidative stress. There is therefore the need to identify the bioactive components to understand the mechanism of action of the extracts of *D. viscosa* in improving cellular antioxidant defense mechanism.

Conclusion

The findings of this study showed that the leaves and stem of *D. viscosa* have strong antibacterial, antioxidant and anticancer properties which justifies the increased consumption of this plant in traditional medicine practiced in Northern Nigeria. Similarly, the study therefore identifies *D. viscosa* as a potential hub for bioactive compound(s) with immense therapeutic potential suggesting the need for further identification of the suspected drug candidates.

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