Pharmacological properties of the ethnomedicinal plant *Dodonaea viscosa*: Anticancer potential and beyond (Review)

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Abstract. Continuous and rigorous assessment of the pharmacological potential of plants is essential for the discovery and development of novel anticancer and other therapeutic agents. Ongoing evaluation also ensures validation of traditional uses while optimizing efficacy and safety. The reporting of these evaluations serves to support innovation of the pharmaceutical landscape to advance evidence-based medicine. Such is particularly important for research in cancer, a highly complex disease that remains a leading cause of mortality worldwide. Numerous conventional anticancer drugs are derived from natural products, highlighting the value of plants as a source of novel compounds with anticancer properties. The medicinal plant, *Dodonaea viscosa* (DV) is an evergreen shrub found in tropical and subtropical regions around the world, with a long history of use in traditional medicine. Different parts of the plant are used in diverse ways for a wide range of ailments by traditional healers. This review provides a comprehensive and updated summary of scientific investigations reporting on the anticancer and other therapeutic potential of DV. Investigations to date have primarily assessed whole DV aqueous and/or organic extracts of various solvents, with only few investigations of fractionated and purified isolates. Using a combination of *in vitro* assays and various animal models, extracts of DV and derivatives show promise as lead compounds for the development of anticancer drugs, including breast, gastric, liver and haematological malignancies. In addition, DV extracts harbour anti-inflammatory, antibacterial, and antioxidant activities This suggests their value as a source of phytochemicals with therapeutic potential.

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Contents

1. Introduction

Cancer remains a leading cause of premature death worldwide, with 9.7 million cancer-related deaths and an estimated 19.3 million new cancer cases in 2022 (1). Africa and Asia experience disproportionate mortality rates compared to incidence rates relative to other regions of the world which can be attributed to multiple factors including delayed diagnosis, unequitable access to quality health care and higher prevalence of infections with cancer-associated pathogens. The majority of patients with cancer choose conventional therapies which include surgery, chemotherapy, and radiotherapy, and for some cancers, immunotherapy, hormone therapy, and other precision-based therapies (2). Most patients with cancer receive a combination of these treatment modalities, for instance, surgery followed by radiotherapy and/or chemotherapy. The effectiveness of the therapy is dependent on a number of interrelated factors, with the type and stage of cancer, and the overall health of the patient being major determinants.

Complementary and Alternative medicines (CAMs) include healthcare practices which are not part of standard and approved medical care, and an estimated 25-84% of patients with cancer use CAM for reasons ranging from personal and cultural beliefs, distrust of modern medicine, or in an attempt to manage the adverse side-effects of conventional treatments (3). The proportion of patients with cancer who primarily use CAMs is higher in developing countries, and this is thought to result from cultural beliefs and practices within specific communities. WHO estimates show that >80% of the population in certain developing countries primarily use CAMs for their health care needs (4). CAM therapies, unlike conventional Western medicine, are not regulated or controlled by any governmental health agency such as the Food and Drug Administration, and although often categorized as 'natural', their use may prove harmful to users due to toxicity and/or incompatibility with conventional treatments if taken concurrently (5).

Nevertheless, natural products have played a crucial role in the development of modern-day cancer therapies and remain an essential source for the discovery and development of new drugs. Due to their scaffold diversity and structural complexity, natural products are structurally optimized by evolution to achieve highly adapted and specific biological functions and as such provide an important foundation to serve as lead molecules in the development of novel and more effective pharmaceuticals (6). With the continued battle of drug resistance and worsening of side effects, there have been renewed efforts in the inclusion of naturally occurring compounds within drug discovery platforms (7). These include derivatives from medicinal plants, which, for centuries, have been utilized by communities to treat an array of illnesses (8).

2. Plant-derived therapeutics

The oldest evidence of the use of plants for therapeutic purposes was found on a Sumerian clay slab from Nagpur, which dates back 5000 years (9). Historical records on the use of plants as powders, teas, tinctures and poultices can be found in Chinese, Indian, Arab and Egyptian cultures (8,10). Some currently in-use chemotherapeutic drugs of herbal origin include: i) Paclitaxel, a terpenoid isolated from the bark and needles of the Pacific yew tree, used in the treatment of several cancers including breast, ovarian, and lung cancer (11,12); ii) etoposide, a non-alkaloid lignan derivative isolated from the rhizomes and roots of the Mayapple, *Podophyllum peltatum/emodi* used in the treatment testicular cancer, non-Hodgkin lymphoma and several other cancers (13,14); and iii) vincristine, a vinca alkaloid isolated from the leaves of the Madagascar periwinkle, *Catharanthus roseus*, used to treat non-Hodgkin lymphoma, breast cancer and leukemia (15,16). Plant-derived bioactive compounds continue to be a valuable source of anticancer drugs and documenting of current knowledge around the use and properties of medicinal plants is therefore useful in the developmental pipeline of these naturally derived drugs.

The evergreen shrub *Dodonaea viscosa* (DV) is widely reported for its medicinal use in complementary medicine, prescribed by 'traditional healers' or alternative medicine practitioners in several countries within the tropical and sub-tropical regions, including Australia, India, Southern African countries, Mexico, Pacific Islands, the Caribbean, Southeast Asia, and parts of the Middle East (Fig. 1A) (17). The bark and leaves are the most commonly used parts of the plant and used as tea infusions for a range of ailments including colds, influenza, digestive disorders, thrush, and measles (18,19). Leaf preparations are indicated for external use to treat skin rashes, topical infections and wounds. To date, the therapeutic properties of the plant and its derivatives, as well as the mechanisms of action, remain largely undefined scientifically, but reports have associated antimicrobial, anti-inflammatory, anti-diarrheal, and anti-proliferative properties to both aqueous and organic extracts of the plant, with biochemical analyses revealing a broad but typical array of phytochemicals including phenols, saponins, tannins and flavonoids (20-28). Among the most abundant phytochemicals found in DV leaves, six are shown in Fig. 1B, purified using various extraction methods, and numerous additional chemical isolates have been reported (20,21). Of those, only few have been investigated for their pharmacological activities to support potential health benefits. Some of the more comprehensive studies are described further in the sections which follow.

3. Laboratory investigations involving DV extracts

Anticancer properties. The antiproliferative effects of DV extracts, most often demonstrated using *in vitro* cell viability assays, have been reported on a range of cancer cell types, primarily of epithelial origin, namely colon, cervical, ovarian, and breast cancers (23-28) (Table I). Studies using the breast cancer cell lines MCF-7 and MDA-MB231 found that DV leaf extracts, prepared using dried leaves ground to a powder and thereafter suspended in solvent, potently inhibited proliferation, via S phase arrest, with an IC_{50} of 75 μg/ml (23,24). In a study assessing crude ethanolic extracts of DV leaves, as well as purified fractions (hexane, chloroform, ethyl acetate, butanol and aqueous fractions), the growth of the established human colorectal adenocarcinoma cell line HT29 was found to be inhibited (25). The mouse 3T3 embryonic non-malignant cell line was also included for comparison. The crude ethanol extract and the chloroform fraction in particular showed significant selectivity towards the cancer cell line, with the chloroform fraction displaying an impressive 12-fold reduced IC_{50} value relative to the 3T3 cells. However, the two major limitations of the study were inclusion of only one representative cancer cell line, and the lack of directly comparable non-malignant cell lines as controls (25). In a subsequent study, the same researchers fractionated and analysed hydroethanolic extracts of DV leaves and identified over 50 individual chemical constituents, a majority of which were flavonoids and diterpenoids (26). They found the hydroethanolic DV extract to be slightly more selective towards the two human colorectal cancer cell lines SW480 and SW620, compared with Chinese hamster ovary cells (CHO-1) and the human benign keratinocyte cell line HaCaT. The effects on cell proliferation and cell death were demonstrated using several standard assays, including analysis of cell morphology using microscopy, induction of apoptosis using Annexin V-PI labelling, and assessment of mitochondrial membrane potential disruptions (26). Extractions using a range of solvents, as well as combinations of solvents, found the flowers and leaves of the plant to yield the highest percentage extract, relative to the stems and roots (27). Notably, the yield varied depending on the solvent type, indicating a richness of phytoconstituents with diverse chemical composition. Except for the flower-derived extract, fractions showed potent cytotoxicity against human leukemic (THP-1) and liver (Hep-G2) cell lines, although selectivity towards cancer cells remains undetermined due to the absence of non-malignant control cells (27). In yet another study, the antiproliferative activity of two purified root extracts, both triterpenoid saponins, was demonstrated against the human ovarian cancer cell line A2780 (28), while fractions from ethanolic crude extracts prepared from leaves showed growth inhibition in the human lung adenocarcinoma cell line A549 (29). These studies are summarized in Fig. 2, and provide strong evidence for the DV plant as a potential lead source of anticancer bioactive phytochemicals, although

Table I. Reported cytotoxicity (*in vitro* and *in vivo*) of *Dodonaea viscosa* extracts on cancer cells.

Cancer type	Experimental approach	Findings	(Refs.)
Breast cancer	MDA-MB232 cell line:		(23)
	• MTT assays	• Inhibited cell viability	
	• Annexin V assay	• Induced apoptosis (increase in late and early apoptotic cells)	
	• Microscopic analysis (cell morphology)	• Decrease in cell density	
	• Mitochondrial membrane potential (Rhodamine 123)	• Decrease in mitochondrial membrane potential	
	• Cell cycle profiling	• Cell cycle arrest in the S phase	
	MCF-7 cell line:		(24)
	• MTT assay	• Inhibited cell viability	
	• Tryphan Blue assay	• Inhibited cell viability	
	• Microscopic analysis (cell density)	• Decrease in cell density	
Cervical cancer	HeLa cell line:		(24)
	• MTT assay	• Inhibited cell viability	
Colorectal cancer	SW480 and SW620 cell lines:		(26)
	• Sulforhodamine B (SRB) colorimetric assay	• Decrease in cell density and proliferation	
	• Annexin V assay	• Induced apoptosis (increase in necrotic cells)	
	• Cell cycle profiling	• Cell cycle arrest in the sub G0/G1 phase (SW620)	
	• Mitochondrial membrane potential [Propidium iodide and DiOC6(3)]	• Decrease in mitochondrial membrane potential	
	• Protein extraction and quantification	• Increase in caspase 3 and p53 expression (SW620)	
	HT29 cell line:		(26)
	• Sulforhodamine B (SRB) colorimetric assay	• Decrease in cell density	
	HCT116 cell line:		(24,35)
	• MTT assay	• Inhibited cell viability	
Liver	HepG2 cell line:		(27,35)
	• Sulforhodamine B (SRB) colorimetric assay	• Decrease in cell density	
	• MTT assay	• Inhibited cell viability	
	In vivo model-adult Wistar male rats:	In hepatocellular-induced carcinoma rats treated with DV AgNPs:	(36)
	• Blood biochemical analysis (ALT, AST, serum albumin, GPx)	• Decrease in ALT, AST and serum albumin, and increase in GPx	
	• Comet assay	• Reduced formation of DNA adducts and minimised damage to DNA structures	
	• Annexin V assay	• Increase in apoptotic cells	
	• Flow cytometry	• Decrease in ROS production	
	• RT-qPCR	• Decrease in *BCL2* and *p53*, and increase in *Bax* gene expression	
Leukaemia	THP-1 cell line:		(27)
	• MTT assay	• Inhibited cell viability	
Ovarian	A2780 cell line:		(28)
	• MTT assay	• Inhibited cell viability	
	SKOV-3 cell line:		(33)
	• MTT assay	• Inhibited cell viability	
Lung	A549 cell line:		(33,34)
	• MTT assay	• Inhibited cell viability	
	• Microscopic analysis	• Decrease in cell density, membrane blebbing, degradation of cell membrane	
	• Live/dead cells assay by high content screening	• Induced apoptosis	
Burkitt lymphoma	Ramos and BL41 cell lines:		(30)
	• WST-1 viability assay	• Decrease in cell viability	

Table I. Continued.

Cancer type	Experimental approach	Findings	(Refs.)
	• Microscopic analysis	• Typical features of apoptosis	
	• Annexin V assay	• Increased apoptosis	
	• Caspase activity assay	• Increased caspase 3/7 enzyme activities	
	• Western blot analyses of apoptotic markers	• Increased cleaved caspase and cleaved PARP-1 expression	
	• Western blot analyses of PI3K/Akt pathway markers	• Reduced p-PDK1 and increased p-PTEN levels expression	

MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; DV, *Dodonaea viscosa*; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; AgNPs, silver nanoparticles; ALT, alanine transaminase; AST, aspartate aminotransferase; GPx, glutathione peroxidase; ROS, reactive oxygen species.

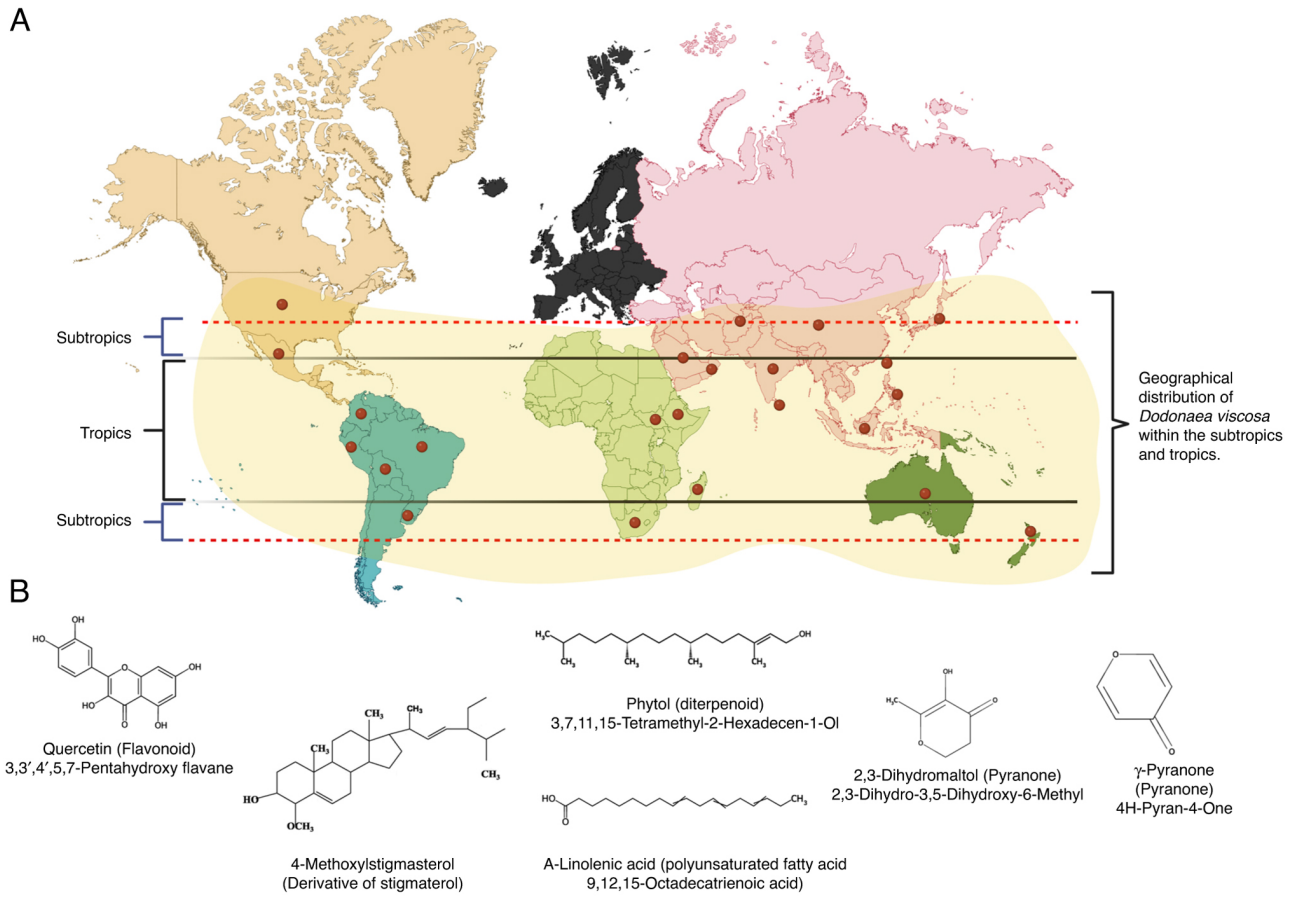

Figure 1. Geographical distribution and major phytocomponents of DV. (A) Worldwide view showing reported geographical distribution of DV in the tropics and subtropics. Alphabetical list of countries where DV is used in traditional medicine: Afghanistan, Australasia and Pacific, Australia, Bolivia, Brazil, China, Colombia, Ethiopia, India, Indonesia, Japan, Madagascar, Mexico, New Zealand, Oman (Arabian Peninsula), Peru, Philippines, South Africa, Sri Lanka, Sudan, Taiwan, Uruguay, Hawaii. (B) Names and structural representation of six of the prevailing compounds isolated from DV leaves using gas chromatography-mass spectroscopy (20,21). DV, *Dodonaea viscosa*.

limitations remain including the robustness of some of the data especially related to selectivity towards malignant cells. To date, few studies have reported on the cellular pathways mediating the cytotoxic mechanism of action of DV extracts. A recent study revealed potent and selective killing of Burkitt lymphoma cells, mediated, in part, through inhibition of the oncogenic P13K/Akt pathway (30).

The use of nanotechnology in the delivery of DV-derived compounds has shown promising results. Advances in nanotechnology research have allowed for improved drug delivery, demonstrating increased efficacy and specificity of treatment, and reduced adverse effects (31,32). As a result, several nano-based treatment modalities have been translated into clinical trials, including silver nanoparticles (AgNPs),

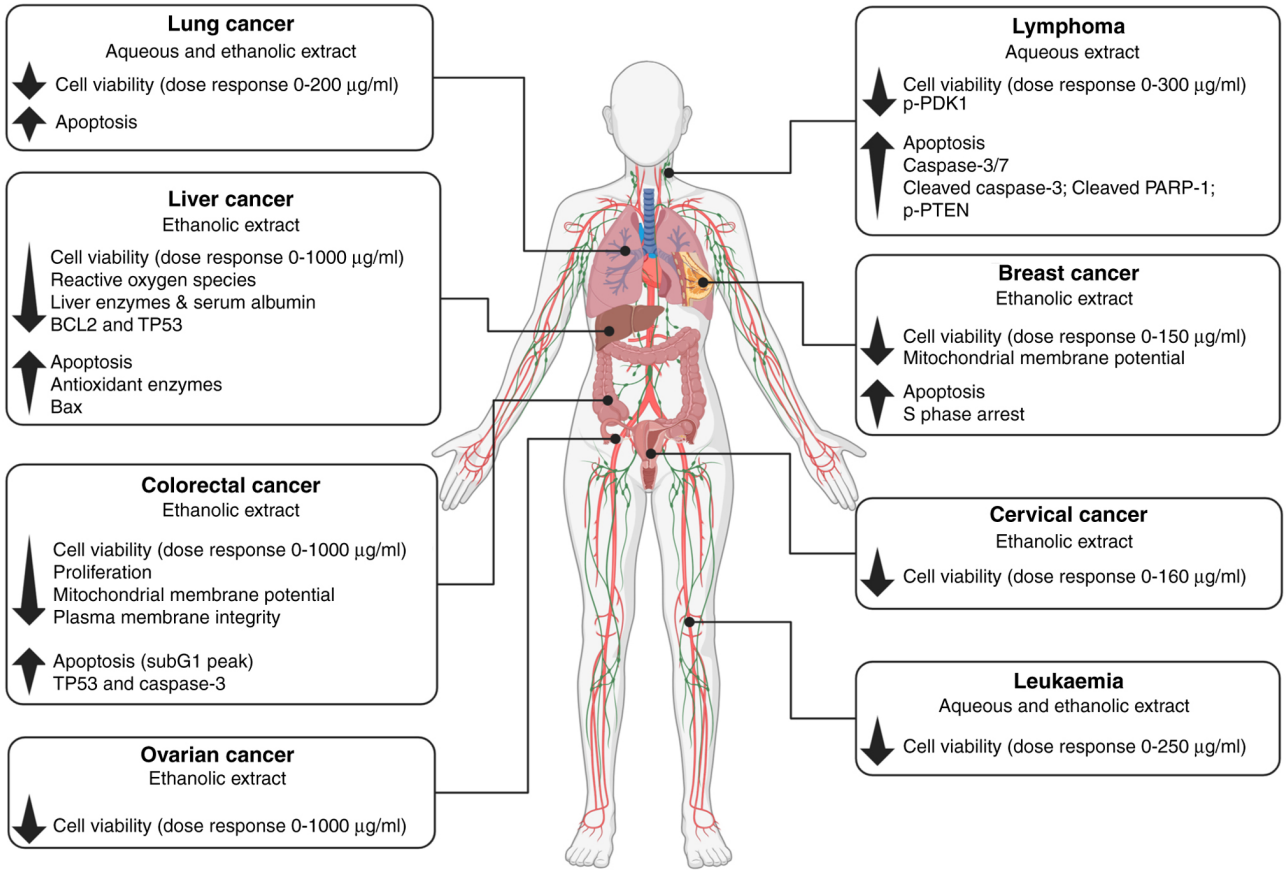

Figure 2. Overview of cancer types in which DV extracts have shown anticancer effects. Infographic showing cancer types where DV extract has been demonstrated to have anticancer effects, including types of extracts, dose treatment range, and altered cancer-associated biological events (23,29,32-36).

which are widely used in clinical applications due to their antimicrobial, antioxidant, antiviral, and antidiabetic properties, and as conjugates with chemotherapeutic drugs (33). Notably, AgNps synthesized from DV leaf extracts have exhibited potent anti-proliferative properties *in vitro* against ovarian (SKOV-3) and lung (A549) cancer cell lines (34,35). In both of these studies, DVE-AgNPs were significantly more toxic to the cancer cells compared with non-cancerous control cells or cancer cells treated with the crude extract alone. Furthermore, cancer cells were markedly more sensitive to AgNPs synthesized from solvents such as petroleum ether, acetone, methanol, and acetonitrile compared with those synthesized from an aqueous solvent (34,35). The use of zinc oxide nanoparticle (ZnO NP) preparations from ethanol-, petroleum ether-, chloroform-, and methanol-derived DV leaf extracts have also yielded promising results, demonstrating significant inhibition of cell viability towards liver (HepG2) and colorectal (HCT-116) cancer cell lines compared with fibroblast cells (3T3), showing superior cytotoxicity relative to Tamoxifen-treated cancer cells (36). ZnO NPs exhibited superior cytotoxicity relative to chloroform-derived DV fractions (IC_{50} values of ZnO NPs: HepG2, 16.4±4 μg/ml and HCT116, 29.07±2.7 μg/ml vs. IC_{50} values of chloroform DV fractions: HepG2, 26.4±3.3 μg/ml and HCT116, 39.8±13 μg/ml) (36).

To date, only a few studies have made use of preclinical models to evaluate the efficacy and safety of DV extracts. Nevertheless, these have yielded promising outlooks on anticancer efficacy, bioavailability and toxicity. For instance, AgNPs synthesized from ethanolic DV leaf extracts inhibited the development of tumours induced by N-nitrosodiethylamine in the liver of Wistar rats (37). Serum levels of enzymatic markers indicative of liver damage, alanine transaminase and aspartate aminotransferase, were significantly reduced, while albumin levels, a marker of less aggressive tumour progression, were reduced. While DNA damage was reduced in hepatic tissues of rats which received the DV-AgNPs, the apoptosis rate was increased. Overall, DV AgNPs exhibited protective effects against liver damage and significantly inhibited hepatocellular carcinoma progression in rats receiving DV extracts compared with controls (37).

Antioxidant activity. Oxidative damage to proteins and DNA resulting from disrupted reactive oxygen species (ROS) homeostasis is a major contributor to genomic alterations that enhance oncogenic phenotypes in cancer cells. Numerous natural products are rich sources of antioxidants able to act as effective scavengers of free radicals and ROS (38). The administration of extracts from DV, both organic and aqueous, proved protective towards carbon tetrachloride (CCL4)-induced hepatotoxicity in rats (39). CCL4 is known to cause liver damage through the formation of ROS, and in that particular study, hautriwaic acid was suggested as the main DV-derived protective compound identified via HPLC fingerprinting (39). In a more recent study (40), through the use of the DPPH (2,2-diphenyl-1-picrylhydrazyl) free radical scavenging *in vitro* assay, stem and leaf extracts of DV were

found to have strong antioxidant activities, which corroborated an earlier study where stem extracts of the plant showed strong scavenging activities (27).

Anti-inflammatory activity. The innate inflammatory response is the first line of defense against damaging agents and invading pathogens, but its effects are mitigated by the use anti-inflammatory medicines to mitigate tissue damage caused by prolonged or excessive responses. Naturally occurring agents with anti-inflammatory properties offer potentially safer and more effective alternatives to synthetic options for managing inflammation. The carrageenan rat paw edema model was used to demonstrate that hydroalcoholic (DVHA) and n-hexane (DVH) extracts from DV leaves were more effective compared with the anti-inflammatory drug indomethacin, in reducing inflammation (41). The study demonstrated that the DVHA and DVH extracts effectively suppressed carrageenan-induced inflammation in rats compared with control rats which either did not receive DV or received indomethacin. In another study, this time using mice ear edema as a model to measure inflammation, a 64% reduction in ear edema was observed in mice receiving DV dichloromethane extracts, compared with a 40% reduction in mice receiving indomethacin (42). A potential mechanism mediating these anti-inflammatory effects was suggested to be through the action of the phytochemical viscosine. Using molecular docking simulations, viscosine was found to impair the activity of lipoxygenase, an enzyme responsible for generating pro-inflammatory mediators and implicated in inflammatory diseases (43). Another notable observation was the potent reduction of nitric oxide production, prostaglandin E2 and tumor necrosis factor-α in the culture medium of lipopolysaccharide-induced murine macrophages (RAW264.7), once again suggesting that extracts from DV possess significant anti-inflammatory activity (43).

Antimicrobial activity. Extracts from the DV plants have been reported to inhibit the growth and biofilm formation of several bacterial and fungal pathogens including *Staphylococcus aureus*, *Streptococcus mutans, Candida albicans, Salmonella typhi, Shigella flexneri, Escherichia coli, Vibrio cholera, Mycobacterium tuberculosis and Pseudomonas fluorescens* (18,27,29,35,44-46). In rats infected with *S. aureus*, those receiving oral administration of ethanolic DV extracts for 30 days had improved kidney histopathology with normal glomeruli and convoluted tubules compared with untreated mice who developed thickening of the wall of renal vessels, infiltrating lymphocytes in the kidneys, and damaged glomeruli (44). Notably, extracts from the DV plant have been shown to display inhibitory effects against strains of *Mycobacterium tuberculosis* (*M. tuberculosis*), the organism responsible for multidrug-resistant tuberculosis which remains a public health concern worldwide. Using the resazurin microtiter assay the anti-mycobacterial efficacy of methyl alcohol and chloroform extracts of DV was assessed against three distinct strains of *M. tuberculosis* namely bg 1972, bg 206, and H37Rv (47). A dose-dependent decrease in the growth of the bacteria was observed, with the most pronounced effect exerted against the H37Rv strain.

The antifungal activity of the acetone-derived DV extract was evaluated against 40 *Candida albicans* (*C. albicans*) strains, 20 of which were isolated from individuals living with HIV and 20 from individuals without HIV (48). Although no discernible difference in effect was observed between the *C. albicans* isolates from the two groups, all strains were potently inhibited by the extracts. Notably, another study demonstrated that planktonic cells of *C. albicans* exposed to acetone DV extracts and DV bioactive compound (5, 6, 8-trihydroxy-7, 4' dimethoxy flavone) could not form germ tubes (49). These findings lend credence to the use of DV extracts by traditional medical practitioners to treat oral thrush and related infections, and suggest that DV may serve as a natural source of antifungal agents. Collectively, these results indicated that DV is a promising source of phytochemicals possessing antibacterial and antimycobacterial properties.

Viral diseases such as Zika, Ebola, AIDS, SARS, MERS, influenza, and pneumonia are major contributors to mortality and disability around the world. In low-income countries, chronic viral infections are attributable to up to 26% of cancer cases, where cancer incidence and related deaths are expected to increase significantly by 2050, highlighting the urgent need for effective prevention and treatment of viral infections (50). In a study by Rashed *et al* (51), the human $CD4^+$ lymphoid cell line C8166 was used to demonstrate DV-induced inhibition of HIV-1 infection. Chromatographic separation of the extract with the highest anti-HIV-1 activity (petroleum ether-derived) identified two compounds, β-sitosterol and stigmasterol, as active antiviral agents (51). In yet another study, the effects of five different extracts from DV leaves were examined against coxsackievirus B3 and rotavirus SA-11 viral infections (52).

Antidiabetic effects. The hypoglycaemic activity of DV leaf extracts (derived from chloroform, methanol, butanol, and aqueous) was analysed in normal and alloxan-induced diabetic rabbits in several independent studies, all of which reported hypoglycaemic effects within 1-2 h after oral administration (53-56). A significant reduction in the blood glucose levels was observed in diabetic rabbits receiving DV compared with those treated with glibenclamide or untreated normal rabbits (53). Prolonged treatment, for 10/15/30 days, potently and consistently reduced blood glucose levels in alloxan-induced diabetic rabbits compared with normal and untreated controls, and a significant increase in plasma insulin levels and a reduction in urea, total cholesterol and triglycerides were observed during the treatment period (54,55). In a different animal model, that of streptozotocin-induced diabetic rats, a significant reduction in blood glucose, pyruvic transaminase, glutamic oxaloacetic transaminase, creatine, and urea was observed in DV-treated animals compared with untreated ones, accompanied by reduced levels of total cholesterol, triglycerides, low-density lipoprotein-cholesterol and pro-inflammatory biomarkers in serum, while no significant change was observed in high-density lipoprotein-cholesterol serum levels (56). Histopathological analysis of the liver and renal tissues from the DV-treated animals showed significant liver protection as evidenced by the regeneration of hepatocytes

with a lack of fatty lobulation and necrosis, and lack of renal tubular necrosis which was evident in animals that did not receive the plant extracts (56). The cumulative findings from these studies provide strong support for the consideration of DV extract as a viable antidiabetic treatment.

Wound healing effects. The application of DV-derived products to assist in wound healing has been reported in alternative therapy, prompting investigation of this potential therapeutic benefit in laboratory-based *in vivo* studies using rats. Ethyl acetate flavonoid-rich fractions extracted from DV leaves were shown to significantly increase levels of hydroxyproline and hexosamine, important constituents of the extracellular matrix, improve collagen formation, and fasten epithelialization and vascularization of wounds, relative to control groups (57). In a separate but similar study using the same *in vivo* model and approach, DV extracts were found to perform similarly to the known and approved antibiotic nitrofurazone in preventing infection and accelerating wound healing (58). These findings warrant further investigations aimed at isolating the bioactive constituents with wound healing and antibiotic properties from the crude extracts of DV.

Other reported therapeutic properties. Extracts from DV leaves were shown to have gastroprotective effects and protect against the development of ulcers in a rodent model (59). Pretreatment with DV hexane extracts blocked the formation of ethanol/indomethacin-induced gastric ulcer lesions in the Charles Wister rats which displayed reduced gastric glutathione levels, inhibition in the accumulation of alkaline phosphatase and increased gastric pH. These effects were similar to those observed in rats treated with the proton-pump inhibitor drug, omeprazole. In a separate study, the anti-diarrheal activity of DV root extracts (alcohol and aqueous) was analysed in male albino mice fed castor oil to induce diarrhea (60). Both alcohol and aqueous DV extracts significantly reduced diarrhea episodes and stool weight in the mice in a dose-dependent manner, similar to what was observed in the groups receiving the anti-diarrheal drug, loperamide. Additionally, the DV extracts were found to be non-toxic to the mice at a dose of up to 2,000 mg/kg. No clinical signs of weakness or other adverse events were observed in the animals after DV treatment (60).

4. Conclusion and future perspectives

The present review provides a comprehensive and thorough overview of the updated published literature reporting on scientific investigations into the therapeutic potential of extracts derived from the DV plant, the latter being traditionally used in ethnomedicine around the world. Collectively, studies assessing anticancer potential (primarily anti-proliferative and antioxidant) provide a strong foundation warranting more comprehensive investigations, with emphasis on obtaining the anticancer bioactive components of DV extracts, as well as the application of systems pharmacology and cheminformatics. Compared with more established medicinal plants such as *Artemisia annua* (source of artemisinin, an antimalarial agent), *Catharanthus roseus* (source of vinblastine and vincristine, used in cancer therapy) and *Taxus brevifolia* (source of paclitaxel, an anticancer drug), only a moderate number of laboratory-based scientific studies have been performed on DV-derived extracts and phytochemicals, and even fewer *in vivo* investigations using animal models. Although numerous DV-derived chemicals have been identified, detailed mechanistic studies aimed at elucidating bioactivities remain sparse, with no reported clinical trials. Nevertheless, the current existing evidence shows considerable promise.

The great diversity in the phytochemical composition of the DV plant extracts as well as the yield thereof appear to be influenced by the choice of extraction solvent. In addition, this diversity is shaped by the specific plant part utilized (leaf/stem/root/flowers). A general trend of decreasing extract yield is observed with a shift in the polarity of the solvent from polar to non-polar, likely due to both the bioavailability and composition of the phytochemicals.

To date, the majority of investigations have employed *in vitro* assays, making use of established cancer cell lines (Table I). Most studies apply crude extracts or fractionated compounds directly onto cells, however where more sophisticated delivery methods have been employed, particularly AgNPs, greater biological impact is observed. This is expected, given the well described advantages of AgNP technology, including improved stability, increased surface-area-to-volume ratio and enhanced uptake. Significantly more preclinical studies are needed, using relevant animal models, to demonstrate the desired anticancer biological effects, but crucially, to gather data on the safety of the novel compounds. Notably, investigations have primarily involved epithelial-derived cancer cells and reveal a gap regarding the potential of DV extracts for the treatment of sarcomas, melanomas, and haematological malignancies.

Since plant extracts represent a mixture of secondary metabolites, it is unsurprising that studies show DV extracts to have antimicrobial, antiviral, and antidiabetic effects, among others (Table II). Such is the case for other plants that have been widely investigated, such as curcumin, cannabis, and galanga. Therefore, the separation of active ingredients and analysis of bioactivity of each compound to identify those with therapeutic promise is essential, however this can be an arduous, costly and lengthy process. While the rich biodiversity enhances the value of such investigations, there can be significant batch-to-batch variability which represents a regulatory hurdle. To minimise this, cultivation and harvest protocols need to be strictly standardized, while maintaining stable processing conditions (61). These factors can translate into quite extended safety evaluations during the drug development process, and once approved, may require ongoing safety monitoring. Another important and often neglected aspect of ethnobotanical studies is the preservation of traditional knowledge and sustainable use of natural products. Nevertheless, plant-derived compounds remain an important source for the development of novel and effective therapeutics, and it is essential to adopt a multidisciplinary framework that brings together conservation programmes, environmentally responsible harvesting strategies, comprehensive scientific and clinical investigations, stringent quality-management standards, regulatory coherence, and ethical governance.

Table II. Reported (non-cancer related) therapeutic biological potential of DV.

Biological activity	Experimental approach	Findings	(Refs.)
Antioxidant	Chloroform and methanol DV extract tested in Wistar rats with liver damage induced by carbon tetrachloride	Reduced CCL4-induced liver injury as evidenced by reduction of serum markers; histopathology and immunochemistry	(39)
	In vitro free radical scavenging assay (DDPH) measuring total antioxidant capacity and reducing power of DV	Increased free radical scavenging ability in the presence of DV extracts	(27)
Anti-inflammatory	Carrageenan rat paw edema model in rats fed hydroalcoholic and n-hexane DV extracts	Extracts suppressed inflammation relative to controls	(41)
	Used a mice ear edema model, inducing inflammation using tetradecanoyl phorbol 13-acetate, and assessed DV dichloromethane-derived extracts	64% reduction in ear edema in mice relative to control mice treated with indomethacin (40%)	(42)
	Molecular docking simulation	Identified viscosine, which impaired the activity of lipoxygenase	(43)
	Measurement of production of nitric oxide and of proinflammatory cytokines in culture medium of lipopolysaccharide-induced murine macrophages (RAW264.7), in the presence of DV extract	Potently reduced nitric oxide production, prostaglandin E2, and tumor necrosis factor-α	(24)
Antimicrobial	Rats infected with *S. aureus* and orally fed with ethanolic DV extract	Improved kidney histopathology with normal glomeruli and convoluted tubules compared with controls	(44)
	Used resazurin microtiter assay to measure anti-mycobacterial efficacy of methyl alcohol and chloroform extracts of DV in three Mtb strains	Dose-dependent decrease in the growth of all three Mtb strains	(47)
	Tested efficacy of HIV-1 infection of the human $CD4^+$ lymphoid cell line C8166	DV isolated active compounds β-sitosterol and stigmasterol as active antiviral agents	(51)
	Infection by coxsackievirus B3 and rotavirus SA-11 viral stocks of MA 104 and GMK cells in the presence of 5 different DV extracts	Methanol crude extract showed the strongest antiviral effect against both viruses	(52)
Antidiabetic	Assessed blood glucose levels in alloxan-induced diabetic rabbits	Rabbits receiving DV had significantly reduced blood glucose levels within 1-2 h. Prolonged treatment produced a potent and consistent increase in plasma insulin levels; significant reduction in urea, total cholesterol, and triglycerides	(53-55)
	Used streptozotocin-induced diabetic rats treated with DV extracts	Significant reduction in blood glucose, serum insulin, and other markers including total cholesterol, triglycerides and low-density lipoprotein-cholesterol	(56)
Wound healing	Used rats with induced excision and incision wounds, applied various DV extracts to wounds	DV-treated animals had improved skin architecture and faster epithelialization and vascularization of wounds	(57)
Anti-ulcer	Rats were pretreated with DV extracts and were thereafter induced to develop gastric lesions	Pretreated rats had reduced gastric glutathione levels, lower accumulation of alkaline phosphatase and increased gastric pH	(59)
Anti-diarrhea	Assessed castor-oil induced diarrhea in mice	Mice fed with DV extracts had significantly reduced diarrhea episodes and stool weight	(60)

DV, *Dodonaea viscosa*; HIV-1, human immunodeficiency 1; Mtb, *Mycobacterium tuberculosis*.

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Authors' contributions

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Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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