



Reflecting on the interesting phytopharmacology of the cosmopolitan *Dodonaea* genus: past, present and future

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Abstract The genus *Dodonaea* is thought to have originated from Australia but it is now found worldwide and in places where the plants occur, they hold ethnobotanical significance. This has prompted phytochemical and pharmacological studies. To date, secondary metabolite profiling has particularly focused on *Dodonaea viscosa* and such studies have shown that flavonoids and terpenoids are the dominant chemical constituents of this taxon. These phytochemicals display a variety of bioactivities such as antitumor, antimicrobial, antioxidant, anti-inflammatory and immunomodulating properties that have been shown mainly in in vitro assays, with a few instances using in vivo animal models. The review aims to provide a systematic and comprehensive overview of *Dodonaea* metabolites and pharmacological studies presented in the past decade. Several databases (Web

of Science, Google and Scopus) were used to compile information presented in this review. A bibliometric analysis of past and present data was conducted via Scopus and this revealed a rising trend in the presence of research related to phytochemistry and pharmacological investigations in the genus. Recent studies show this species as a source of new chemical entities, some of these from the clerodane diterpenoid, and, labdane diterpenoids groups. A set of triterpenoids, now called vistriterpenoids was recently isolated from *D. viscosa*. This review largely focuses on the secondary metabolites but *Dodonaea* species are also known to be rich in primary metabolites which are also thought to impart pharmacological actions. An increasing body of knowledge is likely to lead to commercialization of extracts of *Dodonaea* species in the natural products industry. However, future studies

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need to focus on better chemical characterization of extracts and increasing our knowledge on the safety and toxicity profiles of these extracts using a diverse range of phytochemical and pharmacological tools.

Keywords Flavonoids · Hop bush · Medicinal plant · Sand olive · Sapindaceae · Saponins · Terpenoids

Introduction

Dodonaea Mill., a genus of approximately 70 species, has a long history of ethnobotanical importance because its members have been recorded as being important in the brewing of beer by early European settlers in Australia, hence the common name of hopbush. Till date, these plants are used as phyto-medicines by aboriginal Australians to treat a wide range of minor ailments including cuts and minor wounds, stings from stingrays and toothache (McDowell 2007). *Dodonaea* species are found in many places throughout the entire world but it has been suggested that the genus likely originated from Australia and became widespread in both tropical and subtropical habitats (Pearman 2002). These plants are interesting as they present as a dio- and monoecious shrub and is a member of the plant soapberry family, the Sapindaceae (Order: Sapindales) (Getie et al. 2003). This family encompasses up to 141 genera, displaying close to 1900 species that are woody/herbaceous plants in the form of shrubs, lianas (or climbing vines), subtropical and tropical trees.

Within this family, *Dodonaea* (subfamily Dodonaeoideae) forms the largest group, and in particular, displays significant economic and ecological benefits. The genus is named after the Dutch botanist and physician, Robert Dodoens (Jackson 1990). Specifically, *Dodonaea viscosa* has been the subject of many pharmacological investigations. The species name of ‘*viscosa*’ refers to the stickiness of the leaf surface which has been studied in terms of its phytochemical composition.

Dodonaea plants are evergreen shrubs that favour growing in more sandy soils (Naidoo 2012). Due to these plants being hyper-variable, *D. viscosa* has thus been categorized into seven sub-species; namely, *D. viscosa* subsp. *angustifolia* (L.f.) J.G. West, *D. viscosa* subsp. *viscosa*, *D. viscosa* subsp. *angustissima*

(DC.) J.G. West, *D. viscosa* subsp. *burmanniana*, *D. viscosa* subsp. *cuneata* (Sm.) J.G. West, *D. viscosa* subsp. *spatulata* and *D. viscosa* subsp. *mucronata*, (Harrington and Gadek 2009). Every sub-species inhabits distinct environments, hence, each one is thus able to withstand varying drought intensities. The key characters that are used to differentiate the sub-species are associated with morphological features, growth habit and distribution (McDowell 2007) (refer to Fig. 1 for their distribution). *D. viscosa* subsp. *viscosa*, which is found along the West and East African coasts, and in Madagascar; and *D. viscosa* subsp. *angustifolia* (L.f.) Benth., that has a more inland positioning, are the two subspecies that occur in Africa. The latter is located in the western regions of the Democratic Republic of Congo and it is also found in Ethiopia and eastern parts of Somalia whereas it has a southern distribution in South Africa. There are populations of this subspecies in Madagascar too (Al-Snafi 2017; Rani et al. 2009; West 1984).

There is currently significant taxonomic confusion with respect to the species of *Dodonaea* due to their cosmopolitan distribution (Christmas 2016). Although this is not the key focus of this particular review, it is worthy to emphasise that morphological characters have largely been used to define the species and subspecies of this genus and only recently have molecular phylogenetic studies been utilized to delineate species (Christmas et al. 2015). The Australian, South African and Madagascar species are thought to belong to a more closely related complex (Harrington 2008). Current subspeciation hypotheses developed for *Dodonaea* based on morphological phenotypes may become redundant in the future, with more in-depth genetic analyses using next-generation molecular technologies that may provide new insights into evolutionary diversification within the group (Christmas et al. 2018; Saina et al. 2018). At the moment, *D. viscosa* is the most comprehensively studied species within the genus *Dodonaea*. This may be due to the fact that it is one of the species that have a global dominance in terms of geographical distribution and uses (Priyadi 2021; Rajeswari et al. 2011). For example, in China *D. viscosa* is the only *Dodonaea* species found, occurring in the Yunnan Province (Niu et al. 2010). In South Africa, which is geographically varied, it is associated with a variety of habitats including fynbos, forest and karroid vegetation (Van

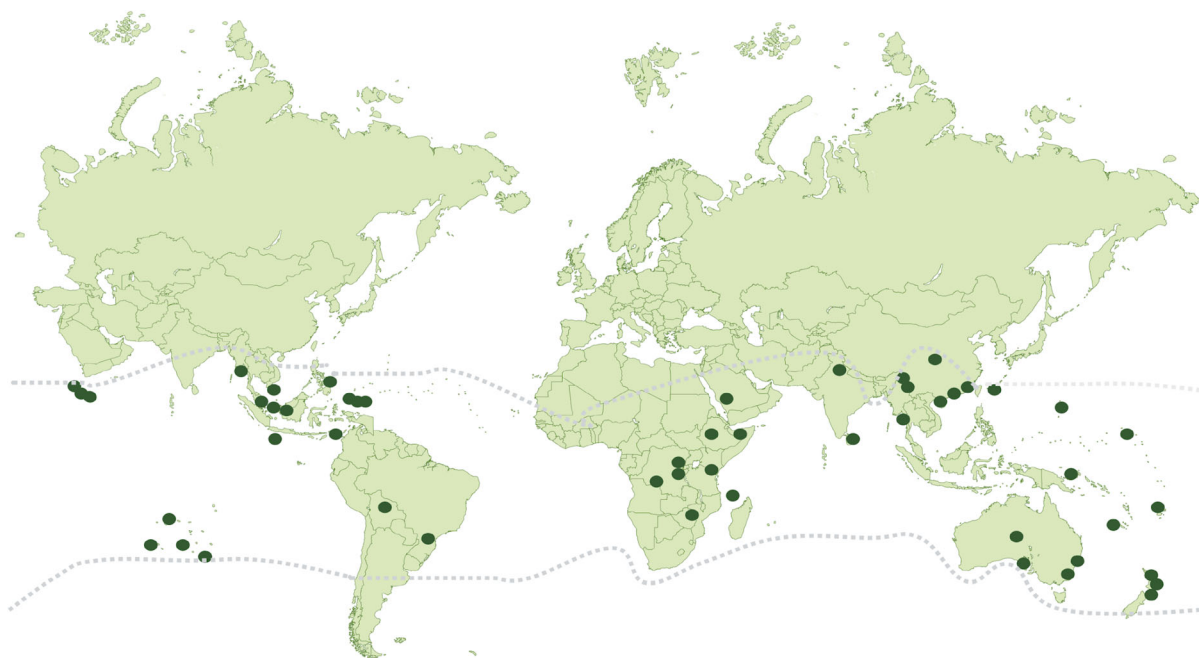


Fig. 1 “Global biogeographic range of *Dodonaea viscosa* (broken lines) and specific locations of previously studied specimens (dots)”. Redrawn using BioRender based on Liu and Noshiro (2003, pp. 533)



Fig. 2 **a** *Dodonaea viscosa* var. *angustifolia* leaves, **b** flowers, **c** papery winged seed capsules

Wyk 2011). However, it does not grow in central South Africa (Van Wyk et al. 1997).

D. viscosa var. *angustifolia* is typically multi-stemmed and leaves are elliptic and narrow (Rani et al. 2009) (Fig. 2a). The leaves are light green in colour and the leaf surface is shiny due to resinous leaf exudates that manifest particularly on the new growth.

It produces small inconspicuous red-greenish flowers which attract insect pollinators during autumn and winter months. (West 1984) (Fig. 2b). After flowering, showy hop-like exaggerated capsules with 3 or 4 rounded wings appear. At first the capsules are green and fleshy, turning yellow green and stained with red or pink (Fig. 2c) (Prendergast and Pearman 2001).

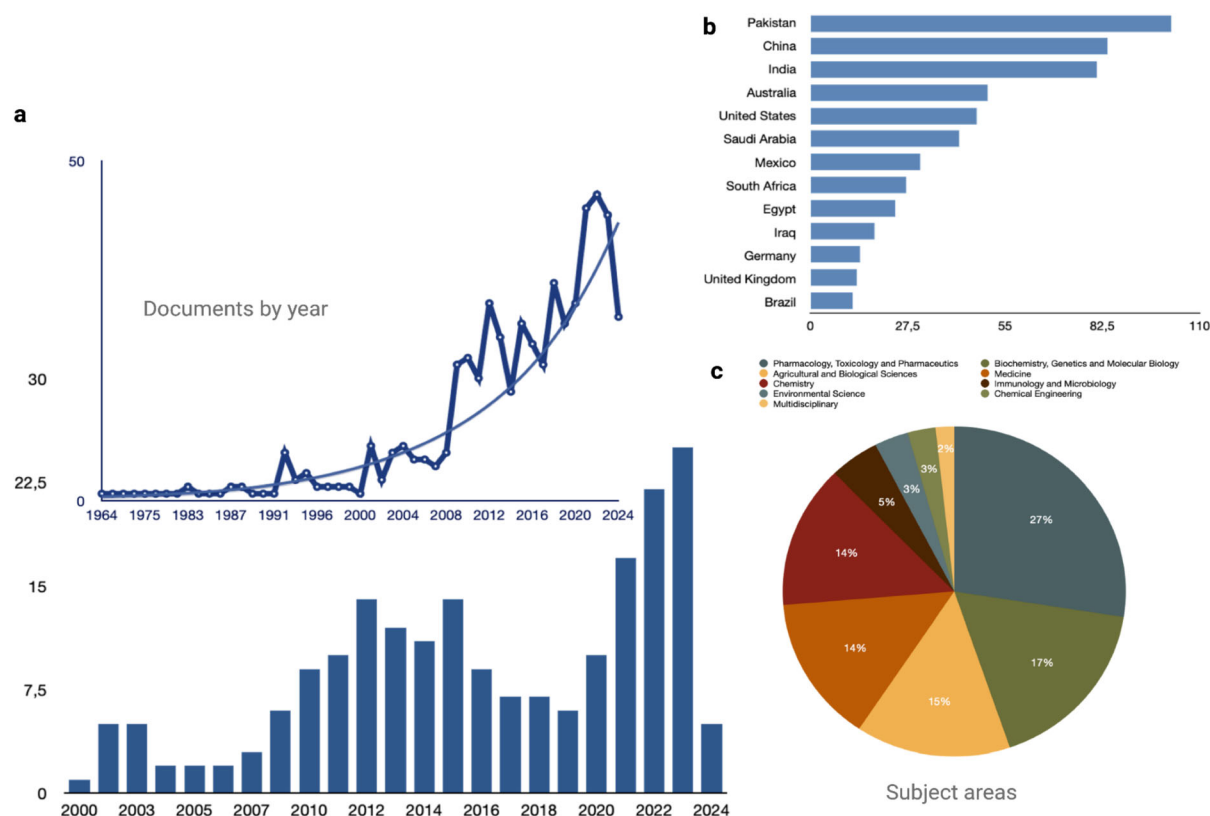


Fig. 3 Bibliometric analysis of published work on *Dodonaea* during the time period of 1980 till 2024. Data generated via Scopus.com

They then dry to a papery brown and each holds 1–3 small round black seeds (Gilman 1999). The plant is a frost hardy, wind and drought-resistant shrub and requires full sun, minimal water and its seeds are easily propagated (Joffe 2001). This hardy plant grows up to a height of about five meters with a diameter of 20 cm (Liu and Noshiro 2003). It is often used to grow hedges and is also planted for the purpose of erosion control for consolidation of sandy environments (Bylsma and Efford 2012). The morphological features of *Dodonaea*, especially leaf shape despite it being highly variable, have largely been used as taxonomic characters to define the group (West 1984) and recent molecular phylogenetic studies showed inadequacies in terms of genetic relatedness of species that call for revision in order to formulate an evolutionary history of the species (Christmas et al. 2018).

The review aims to provide a systematic and comprehensive overview of *Dodonaea* metabolites and pharmacological studies presented in the period

since 2010 till present, with a major focus on new research findings in the past 5 years. This review largely focuses on the specialised (or secondary) metabolites but *Dodonaea* species are also known to be rich in primary metabolites which are also thought to impart pharmacological activities.

Research investigations with a focus on *Dodonaea* species have largely centred around *D. viscosa* since the 1980 (Fig. 3a) and in the past two decades, a large body of research articles has been published leading to an exponential rise of this work in the primary literature in the more recent past. Although, the reviews of Al-Snafi (2017), Beshah et al. (2020), Hossain (2019) and Vishnupriya et al. (2022) have focused on *D. viscosa*, this current review aimed to provide a comprehensive and in-depth update by using an exhaustive review method to identify current trends, knowledge gaps, and new research findings that are fast developing. This was viewed as being critical for building a foundation that may lead *D. viscosa* and its related sister species from its

exploitation as a traditional medicine towards its development for pharmaceutical, cosmeceutical, nutraceutical and agrochemicals industries. The intention of this particular review was to contribute to enhancing existing literature and include the most current contributions that have also appeared in the periods of 2020 till 2024. Such contributions were not only peer-reviewed articles but also technical reports, patents and other literature sources that were focused on the ethnobotany, pharmacology and phytochemistry of the genus, *Dodonaea* that were not necessary included in previous reviews. This particular study also showcases a quantitative bibliometric analysis of past research (Fig. 3) and highlights future directions that may assist in developing medicinal ingredients from *Dodonaea* extracts. We include data on other related species and sub-species that are also now peaking scientific interest. An increasing body of knowledge is likely to lead to commercialization of extracts of *Dodonaea* species in the natural products industry.

Methodology

A review on the literature in terms of *Dodonaea viscosa* was conducted using the Google Scholar, Web of Science and Scopus search engines, following the methods of Masondo and Makunga (2019). For purposes of this literature review, the literature resources were custom filtered for the last decade between years from 2013 up until 2024. Keyword searches included ‘*Dodonaea*’, ‘*Dodonaea viscosa*’, with each of these accompanied by the following words: ‘phytochemistry’, ‘ethnobotany’, ‘terpenoids’, ‘flavonoids’, ‘saponins’ ‘metabololites’, ‘in vivo’ and ‘in vitro’. Data generated using Scopus enabled for a bibliometric analysis of published work during the time period of 1980 till 2024 (Fig. 3a, line graph) and a bar chart was generated with data from 2000 till 2024 that indicates the number of documents published per year. Using this approach, the countries that are most prolific in producing research articles and the subject areas that are most prominent currently were identified (Fig. 3b and 3c). Literature sources were treated according to the flow diagram indicated in the form of a PRISMA chart (Fig. 4). Two databases were used namely Web of Science and Scopus, one website (Google Scholar), two books Van Wyk (1997) and

Van Wyk et al. (2009) and one patent from Makunga and Engelbrecht (2019). ‘Records excluded’ were those resources omitted, as they were considered out scope for this review (did not detail keyword searches and concepts). Reports that were not sought for retrieval, included reports where references that cover subject matter about *Dodonaea* were cited but the reports themselves were centered around a different subject. Reports that were covering subjects that include genetics, physiology, phytoremediation, anatomy, studies focused on environmental impacts on the plant and other concepts that did not not fall in line with the phytochemistry and pharmacology of *Dodonaea* species were regarded as out of scope and therefore excluded and not eligible to be included in the study. ChemDraw Professional (version 16.0) was used to construct figures of chemical structures.

Results and discussion

In the past, studies were mainly intending to generate pure chemical isolates from *D. viscosa* and provide structural elucidation information for these pure isolates. These studies were thus limited in their depth as these chemical isolates were not necessarily always investigated for their pharmacological activities. Nowadays, multidirectional approaches in studying *D. viscosa* have become very useful and subject areas that are currently dominating the literature include pharmacology and toxicology, biochemistry, genetics and molecular biology, and agricultural sciences (Fig. 3c). Such studies are allowing for a better understanding of the interconnectivity of traditional uses, biological activities and possible health-beneficiation that is linked to the medicinal ingredients of *D. viscosa*. Experiments that also involve the other *Dodonaea* spp. have become more popular. Nanotechnology is also being used as a potential drug delivery system for *Dodonaea* extracts should they become commercialised. The work of Nirmala et al. (2024) exploits a ‘green chemistry’ approach to generate nanoparticles of from *D. viscosa* that have bioactivity against inflammation. There are also new developments linked to advancements in metabolomics technologies that are now allowing for a better characterisation of extracts (Kaigongi et al. 2020). Recent studies have applied network pharmacology and computational biology to better understand the

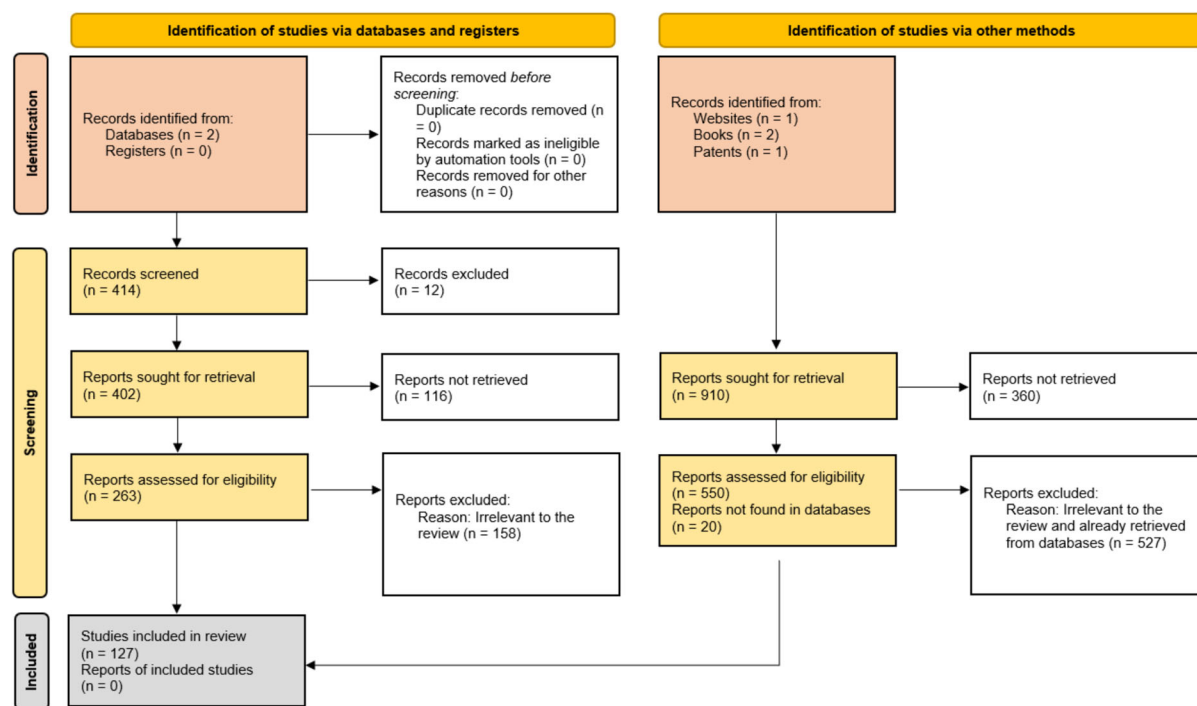


Fig. 4 Systematic review PRISMA flow diagram. (Page et al. 2021)

potential pharmacological activity in silico of various phytochemicals found in *Dodonaea* spp. These approaches are useful as part of the drug discovery value chain for in silico screening prior to in vivo validation of data using animal models which may prove expensive and also the use of a large sample size of animals has ethical considerations. Examples of such studies are found in the work of Rehman et al. (2022) for anti-rheumatic activity and Alamri and ul Qamar (2023) explored the use of computational biology to identify anti-inflammatory phytochemicals of *D. viscosa*. Using a diabetes model, Uddin et al. (2018) showed the isolation of phytochemicals of *D. viscosa* that were inhibiting protein tyrosine phosphatase 1B which is implicated in the regulation of insulin. Recent work is thus providing a more holistic understanding of the pharmacological actions of *Dodonaea* extracts whilst providing empirical data validating the broad range of uses of this genus in traditional medicine. Because the extracts are highly complex, it is becoming clearer that there are still many unknown compounds that are synthesised by these plants and the main bioactive compounds are still not necessarily known. The richness of the

extracts in both terpenoids and phenolics has led to their popularity as phytomedicines.

Ethnobotany of *D. viscosa*

The ethnobotany of *D. viscosa* is very rich as different cultures throughout the world have exploited this medicinal species. In India, for example, the leaves are used for various ailments including hemorrhoids, gout, bone fractures, rheumatism and even snake bites (Venkatesh et al. 2008). There has been a concerted effort to validate claims linked to its traditional medical uses and studies have shown *D. viscosa* to possess various biological activities: (1) antioxidant and antimicrobial (Patel and Coogan 2008; Teffo et al. 2010) (2) anti-inflammatory (Khalil et al. 2006), (3) gastro-protective (Arun and Asha 2008); (4) analgesic, laxative, antiviral, spasmolytic, vasoconstrictive and hypotensive (Venkatesh et al. 2008), and (5) anti-malarial effects (Amelo, et al. 2014; Mengiste et al. 2012). Apoptotic activity against various cancers has also been shown (Cao et al. 2009; Forestrania et al. 2016; Makunga and Engelbrecht 2019). Other parts of the plant have also been shown to be important as seen

in Yirga (2010) where it was reported that *D. viscosa* fruits collected from Northern Ethiopia, are used as a treatment for malaria and dry or fresh fruits are combined with honey for culinary purposes. In Mexico, the plant is also used to alleviate inflammation, pain and rheumatism, hence the motivation to study purified compound(s) from *D. viscosa* for anti-inflammatory effects by Salinas-Sánchez et al. (2012) using in vivo animal models. Other studies have shown that *D. viscosa* is effective as an immunomodulatory as well as having anti-HIV-1 bioactivity (Jagtap et al. 2011). In South Africa, the association of *D. viscosa* var. *angustifolia* with the fynbos habitat of the Cape Floristic Region highlights the interesting cultural significance of the plant species in the Cape region (Philander 2011) as it is one of those species that are popular in a variety of polyherbal remedies and included with other medicinal plants by herbalists (Zonyane et al. 2013). This species has an extensive history in its use as a traditional Khoi remedy to treat influenza, fever, inflammation, tuberculosis and a general immune boosting tonic in the Cape region of South Africa (Philander 2011; Van Wyk 2008). Similarly to other places, a decoction is prepared by placing the leaves in boiling water, steeped and then administered for the respective ailments (Table 1). In places such as Ethiopia, cancers and lymphatic swelling diseases are amongst the batch of diseases *D. viscosa* is used for (Tauchen et al. 2015).

D. viscosa var. *angustifolia* is not only cultivated for use as traditional medicine but also its wood is used for various tools, brooms, and weapons such as spears and clubs (Prendergast and Pearman 2001; Burton 2012). As the roots have a firm hold in soil, the shrub is used as a windbreak for prevention of soil erosion in hot, dry areas (Jabeen et al. 2009).

The global medicinal significance of *D. viscosa* has encouraged phytochemical analyses of the plant and several studies have already contributed to an ever growing list of identified chemicals found in *D. viscosa* (Mostafa et al. 2014; Muhammad et al. 2012; Muhammad et al. 2015; Olivier et al. 2016; Rani et al. 2009). The polyphenolic and saponin content that represent a substantial fraction of the phytochemical profile of *D. viscosa* has led to a species with exceptional bioactivity (Kaigongi et al. 2020). In the past 10 years, new terpenoids that are uniquely found in *D. viscosa* highlight new knowledge about its phytochemistry and pharmacology and have furthered the movement to better understand the effects of phytoextracts not only in in vitro assays but also using in vivo models. Based on new research in the literature, we summarize the phytochemistry and bioactivity studies on *Dodonaea*, where a record of chemical information exists and highlight the current gaps and point out areas for future research that would benefit natural products research which could possibly lead to drug development.

Table 1 Traditional medicinal uses of *D. viscosa*

Ailments	Plant part used	Method of administration	References
Fever	Leaves	Decoction	van Wyk et al. (1997)
Sore throat	Leaves	Gargle	van Wyk et al. (1997)
Oral thrush	Leaves	Gargle	van Wyk et al. (1997)
Rheumatism	Leaves	Decoction	Venkatesh et al. (2008)
Colds and influenza	Leaves	Tincture	Venkatesh et al. (2008), van Wyk et al. (1997)
Skin rashes	Leaves	Applied externally as a Paste	Venkatesh et al. (2008)
Gout	Leaves	Decoction	Venkatesh et al. (2008), Teffo et al. (2010)
Irregular menstruation and dysmenorrhea	Leaves	Decoction	Teffo et al. (2010)
Stimulation of breastmilk production	Leaves	Tincture	Mostafa et al. (2014)
Cough	Leaves	Steam inhalation	Samavati and Manoochehrizade (2013)

Table 2 Chemical compounds isolated from *Dodonea* based on the literature over the last 10 years

Terpenoids		
Chemical Name	Country/Region	Reference
1. Dodoneaside A	Madagascar/Africa	Cao et al. 2009
2. Dodoneaside B	Madagascar/Africa	Cao et al. 2009
3. Vishautriwaic acid	China/East Asia	Huang et al. 2010
4. Visclerodol acid	China/East Asia	Huang et al. 2010
5. 2,18-dihydroxylabda-7,13(<i>E</i>)-dien-15-oic acid	Cameroon/Africa	Wabo et al. 2012
6. 13,17-epoxy-13-methyl-15-oxo-labda-7-ene	Australia	Simpson et al. 2012
7. 17-hydroxy-13-methyl-labda-7,13 <i>Z</i> -diene-15-oic acid	Australia	Simpson et al. 2012
8. 13-methyl-17-oxo-labda-7,13 <i>Z</i> -diene-15-oic acid	Australia	Simpson et al. 2012
9. <i>ent</i> -15 ξ -ethoxy-labdan-3 α ,8 β -dihydroxy,13(14)-en-15,16-olide	Brazil/South America	De Oliveira et al. 2012
10. <i>ent</i> -16 ξ -hydroxy-labdan-3 α ,8 β -dihydroxy,13(14)-en-15,16-olide	Brazil/South America	De Oliveira et al. 2012
11. 8 β -hydroxy-3-O- β -d-glucopyranosyl- <i>ent</i> -labda-13-en-15,16-diol	Brazil/South America	De Oliveira et al. 2012
12. Dodonic acid	Kenya/Africa	Omosa et al. 2014
13. 2 β -hydroxyhardwickiic acid	Kenya/Africa	Omosa et al. 2014
14. (<i>ent</i> -3 β ,8 α)-15,16-epoxy-13(16),14-labdadiene-3,8-diol	Kenya/Africa	Omosa et al. 2014
15. Dodovisnoid A	China/East Asia	Zhang et al. 2016
16. Dodovisnoid B	China/East Asia	Zhang et al. 2016
17. Dodovisnoid C	China/East Asia	Zhang et al. 2016
18. Dodovisnoid D	China/East Asia	Zhang et al. 2016
19. Dodovisnoid E	China/East Asia	Zhang et al. 2016
20. Dodovisnoid F	China/East Asia	Zhang et al. 2016
21. Dodovisnoid G	China/East Asia	Zhang et al. 2016
22. Vistriterpenoid A	China/East Asia	Wang et al. 2018
23. Vistriterpenoid B	China/East Asia	Wang et al. 2018
24. Dodovisdimers A	China/East Asia	Zhao et al. 2021
25. Dodovisdimers B	China/East Asia	Zhao et al. 2021
26. Dodovisdimers C	China/East Asia	Zhao et al. 2021
27. Saponin A (DVSA)	China/East Asia	Yu et al. 2022
28. (6 <i>S</i> , 9 <i>R</i>)-vomifoliol-9- β -D-glucopyranosyle (1-3)-O- α -L-rhamnopyranoside	Saudi Arabia/SW Asia	Siddiqui et al. 2023
Phenolics		
29. 5,7,4'-trihydroxy-3,6-dimethoxyflavone	South Africa/Africa	Teffo et al. 2010
30. 5,7,4'-trihydroxy-3',5'-di(3-methylbut-2-enyl)-3,6-dimethoxyflavone	China/East Asia	Niu et al. 2010
31. 5,7,4'-trihydroxy-3'-(4-hydroxy-3-methylbutyl)-5'-(3-methylbut-2-enyl)-3,6-dimethoxyflavone	China/East Asia	Niu et al. 2010
32. 5,7,4'-trihydroxy-3'-(3-methylbut-2-enyl)-3-methoxyflavone	Australia	Simpson et al. 2011
33. 5,7-dihydroxy-3'-(3-methylbut-2-enyl)-3,4'-dimethoxyflavone	Australia	Simpson et al. 2011
34. 5,7,4'-trihydroxy-3',5'-(3-methylbut-2-enyl)-3-methoxyflavone	Australia	Simpson et al. 2011
35. 5,7-dihydroxy-3,6,4'-trimethoxy-3'-(4-hydroxy-3-methylbut-2-enyl)flavone	Cameroon/Africa	Wabo et al. 2012
36. 4',5,7-trihydroxy-3-methoxyflavone (isokaempferide)	Kenya/Africa	Omosa et al. 2014
37. 3,4',5,7-tetrahydroxy-6-methoxyflavone	Kenya/Africa	Omosa et al. 2014
38. Visconata	Pakistan/South Asia	Uddin et al. 2017
39. 3,3',4',5,7-pentahydroxyflavan	Oman/West Asia	Al Habsi and Hossain 2018
40. 3,5,7,3',4'-pentahydroxyflavone	Oman/West Asia	Al Bimani and Hossain 2020
41. Viscomarfadol	Saudi Arabia/SW Asia	Almarfadi et al. 2024

Phytochemicals

A suite of unique secondary metabolites is attributed to the sticky residue found on the surface of leaves in *D. viscosa* but these plants also show an interesting chemistry when different solvents are used as extrac-

tants. A wide range of extracts have been studied and chemicals found in the species are listed in Table 2. Different plant parts also exhibit variable

phytochemistry. In general, these secondary metabolites include flavonoids, di- and triterpenoids, saponins, and other phenolic compounds (Rani et al. 2009; Venkatesh et al. 2008). The contribution to the medicinal attributes of all of these secondary metabolites within *D. viscosa* is thought to be that of a synergistic effect, rather than individual chemical entities producing an effect. Some of the earliest chemicals identified in this plant are viscosol, dodonic

acid, hautriwaic acid and 5,7,4'-trihydroxy-3,6,-dimethoxyflavone (Sachdev and Kuishreshth 1983; Van Heerden et al. 2000; Van Wyk 2009) (refer to Fig. 5 and 6 for some of the structures). Although medicinal uses of *Dodonaea* spans millennia, there is currently limited scientific information regarding the key metabolites that play a significant role in terms of the medicinal value of this species and related taxa (Omosa et al. 2014). The secondary metabolite constituents of *D. viscosa* leaf surface exudates have piqued the interest of natural product chemists since the 1970s and studies have thus revealed that the plant constitutes mainly methylated flavonoids and diterpenoids having labdane and clerodane skeleton structures (Ghisalberti 1998). Labdane diterpenoids are bicyclic diterpenes whereas the clerodanes are related to the bicyclic labdane diterpenes having a chloroplastic biosynthesis in plants (Hu et al. 2021). From a biosynthesis perspective, the labdane- and clerodane-type diterpenes are distinguished through enantiomeric methyl and hydride shifts (Simpson et al. 2012). These sub-classes of diterpenes are found widely possessing notable bioactivities (Table 3), including antifeeding function against insects indicating their evolutionary-derived ecological roles. As shown in Table 3, these terpenoids also possess antibacterial, antiprotozoal, antifungal, enzyme inducing, anti-inflammatory and immunomodulatory effects in animal cells.

Terpenoids

Isopentenyl diphosphate (IPP) is a precursor having a 5C unit that is key in building a wide array of terpenoids and both the cytosol via the mevalonic acid (MVA) pathway and the plastidal production through the methylerythritol phosphate (MEP) biosynthesis leads to different terpenoids (Sawai and Saito 2011). The IPP is used to generate monoterpenoids, diterpenoid, and tetraterpenoids are biosynthesized using the MEP pathway, whereas triterpenoids and sesquiterpenoids are manufactured via the MVA pathway. Jefferies et al. (1981) were amongst the first to study the diterpenoids of *Dodonaea*, focusing on *D. petiolaris*. Since the review of Rani in 2009, new molecules have been elucidated in different extracts of *D. viscosa*. For example; studies of Simpson et al. (2012), De Oliveira et al. (2012) and Wabo et al. (2012) have contributed to the purification of labdanes

(Fig. 5 depicts some of the structures). On the other hand, Cao et al. (2009) resolved the structures of oleanane-type triterpenoid saponins, termed dodonaeaside A and B, isolated as crystalline samples from *D. viscosa* roots of Madagascan origin. Omosa et al. (2014) reported on structures of dodonic acid, 2 β -hydroxyhardwickiic acid and (*ent*-3 β ,8 α)-15,16-epoxy-13(16),14-labdadiene-3,8-diol diterpenoids (Table 2) which are surface exudates of *D. viscosa*, extracted into acetone by leaf surface dipping for 15 s, followed by a structure–activity relationship study to better understand the effects of these phytochemicals on antibacterial activity. Triterpenoids are also represented in *D. viscosa* (Cao et al. 2009). In plant cells, they possess diverse roles functioning as chemical barriers to prevent excessive dehydration, offering biotic and abiotic protection and they have aseptic properties against microbial pathogens (Cárdenas et al. 2019). The molecular characterization of triterpenoids is not necessarily easy due to their complicated chiral structures that have many isomer positions (Brill et al. 2017). The cyclization of 2,3-oxidosqualene by the enzyme oxidosqualene cyclase is crucial regulatory step diversifying the triterpenoid biosynthesis leading to many different structural groups (for a review refer to Sawai and Saito (2011)). The following are new clerodane diterpenoid isolates: vishautriwaic acid and visclerodol acid in *D. viscosa* from Yunnan (China) by Huang et al. (2010). Methylodonates also contribute to the special phytochemistry of *D. viscosa* and these chemicals are also clerodane diterpenoids (Ortega et al. 2001).

Apart from *D. viscosa*, other *Dodonaea* species with similar clerodane structures in the leaf resin are *D. attenuata* and *D. boroniaefolia* (Moussa 2015). New labdane diterpenoids were isolated from *D. viscosa* ssp. *spatulata* by Olivier et al. (2016) by flash column chromatography on silica gel, together with a Fischer esterification that led to six pure compounds at a yield of (0.3 to 0.5% w/w). Spectroscopic data based on ¹H, ¹³C NMR and IR was used to conclude on the structures of the purified molecules. Before this time, seven labdanes were known to exist in extracts of *D. viscosa*. Zhang et al. (2016) isolated seven novel clerodane derivatives (aptly named dodovisnoids A-G). These authors propose that dodonolide is a precursor molecule for the dodovisnoids that they isolated. Furthermore, one of the chemicals, dodovisnoids A, is thought to be biogenetic derivative of 5,10-

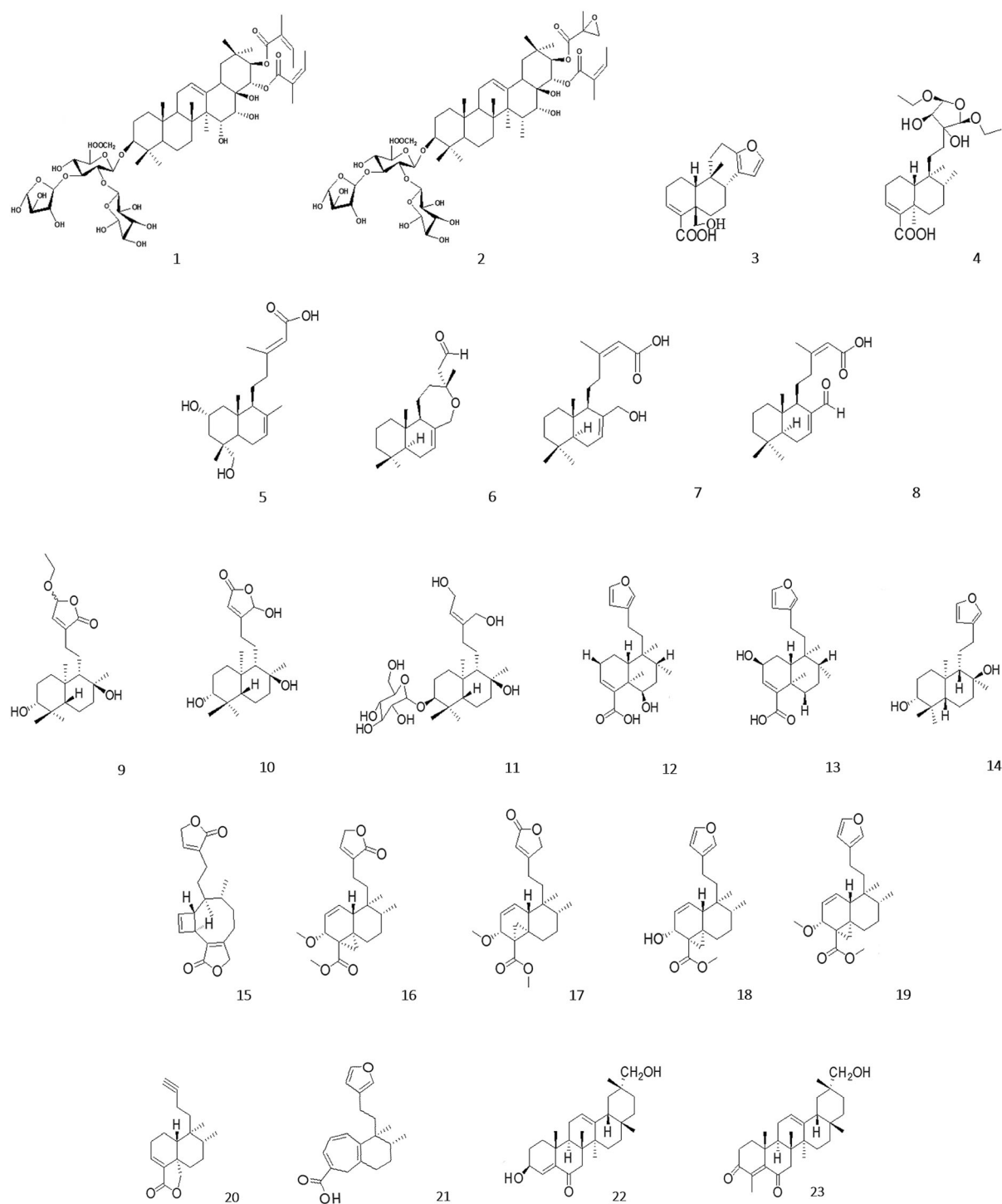


Fig. 5 Chemical structures for some of the new terpenoids isolated from different varieties of *Dodonaea* based on literature

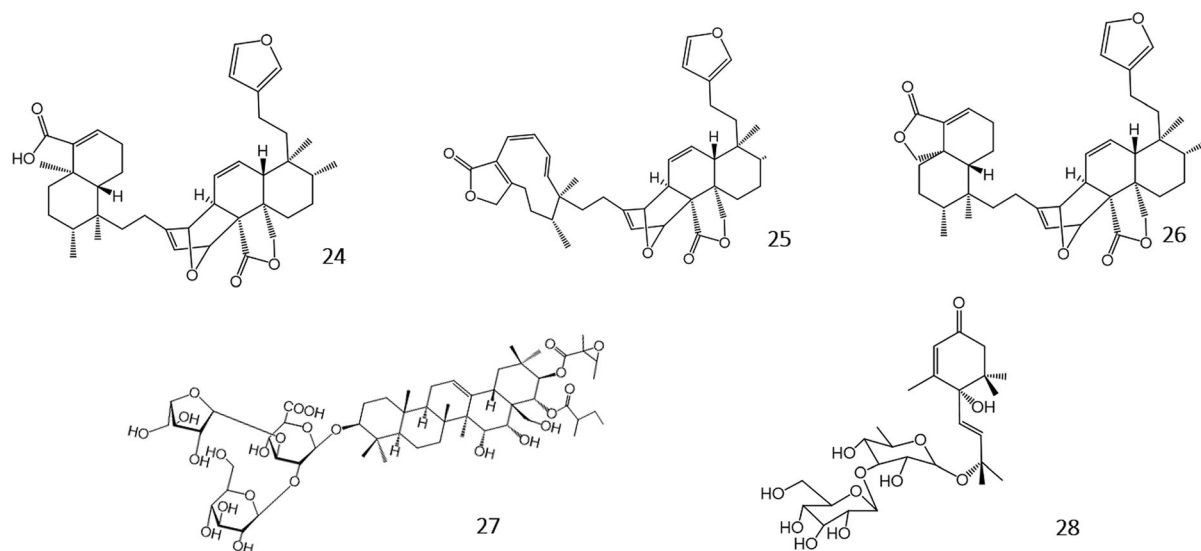


Fig. 5 continued

secoclerodane and three of the compounds examined in that paper had cyclopropyl-modified clerodane skeleton which is apparently rare and that has been uncovered in methyl dodonates produced by *Dodonaea* species. Some of the structures, dodovisnoids A, B and F, were resolved using X-ray crystallography and four chemical isolates exhibited antiviral activity. Six triterpenoids including two new vistriterpenoid compounds were recently isolated from plants growing in the Fujian Province (Wang et al. 2018). These new structures, determined using HR-ESI-MS, HSQC and HBMC spectral analysis, were confirmed to be 24-noroleanane triterpenoids. One of the chemicals was assigned a molecular formula of $C_{29}H_{44}O_3$ (m/z 463.3185) and NOESY correlations confirmed its oleanane skeleton backbone and it was then termed vistriterpenoid A (or 6-oxo-24-nor-4,12-oleanadien-3 β -,29-diol). The other triterpenoid, vistriterpenoid B ($C_{29}H_{42}O_3$; m/z 461.3022 ($M + Na$) $^+$, $C_{29}H_{42}NaO_3$) was confirmed to be 3,6-dioxo-24-nor-4,12-oleanadien-29-ol and both these chemicals and other previously isolated triterpenoids (i.e. epifriedelinol, cavalerol, olean-12-ene-3 β -,29-diol and 3 α -hydroxytirucalla-7,24-dien-21-oic acid) were tested for in vitro activity in the PTP1B inhibition antidiabetic assay.

The new structures isolated by Wang et al. (2018) provide a set of biomarkers that can aid in the

chemotaxonomy of *D. viscosa*. Further purification of 24-noroleanane triterpenoids was carried out using ethanol extractions (95%; v/v) which were then partitioned with ethyl acetate via Diaion HP-20CC column, generating six fractions.

From 11.0 kg of experimental plant material, 30 mg of the vistriterpenoid A and 12.0 mg of vistriterpenoid B (both as white dry powders) were generated (Wang et al. 2018). By using pressurized hot water extraction (PHWE) on the leaves of *D. viscosa* ssp. *spatulata*, a series of carboxylic acid-containing *ent*-labdane diterpenoids could be isolated (Deans et al. 2018). Various fractions generated using flash chromatography with ethyl acetate/hexane (0 to 100%); MeOH/ CH_2Cl_2 (0 to 10%) for 8 min and MeOH/ CH_2Cl_2 (10 to 20%) for 4 min to produce fractions with chemicals of different polarities, led to eight different chemical isolates that were further studied using 1H , ^{13}C , and 2D NMR spectroscopy and led to two new *ent*-labdanes from *D. viscosa* samples (Deans et al. 2018). It is clear that isolation of new chemical entities from *D. viscosa* is not yet exhaustive and there is further scope for new terpenoid compounds and their derivatives to be obtained from these plants.

Table 3 Summary of former study results regarding pharmacological activity of various metabolites produced by *Dodonaea**

Sample type or compound	Identification of compounds and structures	Assays used	Overall results summary and MIC values	Country/Region	References
Plant extracts					
Acetone extracts		Effect on the biofilm formation. Scanning electron microscope. Effect of the crude plant extract on the germ tube formation.	Decrease in percentages of germ tube formation in <i>Candida albicans</i> at 3.125, 1.56, and 0.78 mg/ml extract and frequency of the germ tube production was reduced by 85.36, 61.91, and 26.27%, respectively.	South Africa/ Africa	Naicker and Patel (2013)
Crude extracts surface exudates of <i>D. angustifolia</i>		Agar well-diffusion method used for evaluation of antimicrobial activity.	Surface exudates had antimicrobial activity against <i>Escherichia coli</i> , <i>Staphylococcus aureus</i> and <i>Bacillus pumilus</i> bacteria and the <i>Saccharomyces cerevisiae</i> fungus at 2500 µg/well.	Kenya/ Africa	Omosa et al. (2014)
Ethanol, methanol extracts		In vivo study on <i>Plasmodium berghei</i> male Swiss albino mice using antimalarial assay and disease progression in the test animals using Peter's 4-day suppressive examination.	At a dose of 300 mg/kg, the ethanol leaf extract reduced the amount of parasites by 77.2% and out of the fractions tested, the hexane and ethyl acetate fractions were effective in reducing parasitemia.	Ethiopia/ Africa	Melaku et al. (2017)
Hexane, chloroform, ethyl acetate, butanol and water extracts		Antioxidant activity using α -diphenyl- β -picrylhydrazyl (DPPH) method.	Hexane extracts had high antioxidant properties (94.41 ± 0.12 percentage inhibition) in the DPPH assay where the least inhibition was detected for a butanol extract.	Oman/ West Asia	Al Habsi and Hossain (2018)
Ethyl acetate, chloroform, petroleum ether, methanol and water extracts		Antioxidant activity using DPPH method. Anti-inflammation activity (proteinase inhibitory effect and inhibition of albumin denaturation).	Methanol extract (200 µg/ml) had the highest scavenging activity (93.57%). Albumin denaturation (85.09%) and proteinase inhibition (67.24%) were recorded for an extract applied at a concentration of 500 µg/ml.	Saudi Arabia/ SW Asia	Nayeem et al. 2019
Ethyl acetate extract of stem bark (EAEDV)		Elevated Plus Maze (EPM) was used to assess CNS effects.	Most significant anti-anxiety effect was with EAEDV at concentrations of 200 mg/kg and 400 mg/kg.	Saudi Arabia/ SW Asia	Rajalakshimi et al. (2019)
Crude extract separated into n-hexane, chloroform, ethyl acetate, n-butanol extracts		Agar well-diffusion method used for evaluation of antimicrobial activity.	Highest inhibition of <i>Streptococcus pyogenes</i> gp <i>B.HVS</i> and <i>S. HVS</i> was seen by 2 mg/ml concentration of ethyl acetate extract and 2 and 1 mg/ml chloroform extracts inhibited <i>S. HVS</i> diameters with 10 and 9 mm respectively for the zone of inhibition.	Oman/ West Asia	Al Bimani and Hossain (2020)
n-hexane, chloroform, ethyl acetate, n-butanol extracts and aqueous fraction		Sulforhodamine B (SRB) test to determine cell viability of HT-29 tumor cell lines from human colon adenocarcinoma.	Chloroform and ethanol extract showed best inhibitory effect on HT-29 cell lines (IC ₅₀ values below 20 µg/mL).	Peru/ South America	Herrera-Calderon et al. (2020)

Table 3 continued

Sample type or compound	Identification of compounds and structures	Assays used	Overall results summary and MIC values	Country/Region	References
Methanolic and chloroform extracts, 10% w/w herbal ointment of the extracts		Wound healing activity in Sprague Dawley rats. Excision and the incision wound model where tensile strength and epithelialization duration were measured.	Methanolic and chloroform extracts both increased speed of epithelization. The period of epithelization for methanolic extract was 12 days, chloroform extract was 14 days and base group 17 days. Methanolic and chloroform extracts showed significantly higher tensile strength than control ($p < 0.001$) and base ($p < 0.01$) groups.	Saudi Arabia/ SW Asia	Nayeem et al. (2021)
Fourteen <i>D. viscosa</i> flower, leaf, stem and root extracts, each prepared with 14 different solvent combinations	HPLC	Chromogenic assays for antioxidant profile Standard brine shrimp lethality, MTT and SRB assays for cytotoxicity potential.	Methanol and ethylacetate stem extract (IC ₅₀ = 23.8 mg/ml) for maximum scavenging potential. Flower and root extracts showed the highest antibacterial potential (85.7% and 71.4% respectively). Ethanol and ethyl acetate (1:1) leaf extract (IC ₅₀ = 95.46 mg/ml) for toxicity against brine shrimps. Antiproliferative activity against cancer cell lines with ethanol and ethyl acetate extracts (1:1) from stem THP-1 (IC ₅₀ = 3.4 mg/ml) and root Hep G2 (IC ₅₀ = 20 mg/ml).	Pakistan/ South Asia	Malik et al. (2022)
Methanolic extract fractionated into n-hexane, dichloromethane, ethyl acetate, butanol, and aqueous		DPPH assay and α -Glucosidase assay Carbonic Anhydrase II Inhibition Assay.	IC ₅₀ values of significant activity were as follows: for (DPPH) assay- EtOAc (IC ₅₀ = 386 ± 1.65 μ g/mL) and n-BuOH IC ₅₀ = (467 ± 1.84 μ g/mL), α -Glucosidase assay- n-BuOH (IC ₅₀ = $1:30 \pm 0:05$ μ g/mL) and n-hexane fractions (IC ₅₀ = $2:04 \pm 0:06$ μ g/mL) and Carbonic Anhydrase II Inhibition Assay- EtOAc (IC ₅₀ = 27.5 ± 3.12 μ g/mL) and MeOH extract (IC ₅₀ = 50.4 ± 2.03 μ g/mL).	Oman/ West Asia	Rehman et al. (2022)
Ethyl acetate fraction from water–ethanol extract <i>D. viscosa</i> ointment (DVFO, 2.5%w/w and 5%w/w)	HPLC	Wound healing activity in Sprague Dawley rats. Excision and the incision wound model where tensile strength and epithelialization duration were measured. Povidone-iodine ointment (5% w/w) as a control. Histopathology analysis and western blots were conducted to determine regulation of collagen type 3 (COL3A1), basic fibroblast (bFGF) and vascular endothelial growth factor (VEGF).	Wound contraction on day 15 in 2.5% w/w (88.88%) and 5.0% w/w (94.89%). DVFO treated groups was significantly higher than the control group. Control group had tensile strength of 319.28 ± 2.59 g, 2.5% w/w DVFO was 557.23 ± 4.79 g and 5% w/w DVFO had 640.48 ± 8.89 g. Upregulation of COL3A, and bFGF protein in DVFO-treated group ($p < 0.01$).	India/ South Asia	Subramanian et al. 2023

Table 3 continued

Sample type or compound	Identification of compounds and structures	Assays used	Overall results summary and MIC values	Country/Region	References
Crude extract	IR, UV, NMR spectroscopy	Transient middle cerebral artery occlusion (MCAO) method.	Significant decrease in pro-inflammatory cytokines TNF α and IL-6, downregulation in NF- κ B gene expression, upregulation of anti-apoptotic Bcl-2 gene expression and downregulation of BAX and caspase-3 gene expression ($P < 0.05$).	Saudi Arabia/ SW Asia	Siddiqui et al. (2023)
Methanolic extract		Protective effects against focal cerebral ischaemia–reperfusion injury using the middle cerebral artery occlusion (MCAO) model.	Improved neurological function by 27.27% and 54.55% and reduced infarct volume by 25.79% and 45.26%, respectively for 150 and 300 mg/kg/day of methanolic extract.	Saudi Arabia/ SW Asia	Almarfadi et al. (2024)
Compounds					
5-hydroxy-3,7,4'-trimethoxyflavone	UV, MS, 1D, 2D, NMR spectroscopy	Agar well-diffusion method used for evaluation of antimicrobial activity.	–	Kenya/ Africa	Omosa et al. (2014)
Kumatakenin	UV, MS, 1D, 2D, NMR spectroscopy	Agar well-diffusion method used for evaluation of antimicrobial activity.	–	Kenya/ Africa	Omosa et al. (2014)
Santin	UV, MS, 1D, 2D, NMR spectroscopy	Agar well-diffusion method used for evaluation of antimicrobial activity.	Most active flavone against <i>Saccharomyces cerevisiae</i> with a MIC value of 3.9 μ g/well and poor antibacterial activity against <i>Bacillus pumilus</i> with a MIC value of 250 μ g/well.	Kenya/ Africa	Omosa et al. (2014)
Penduletin	UV, MS, 1D, 2D, NMR spectroscopy	Agar well-diffusion method used for evaluation of antimicrobial activity.	Some inhibition against <i>Saccharomyces cerevisiae</i> with a MIC value of 125 μ g/well and at 500 μ g/well and some inhibition against <i>Bacillus pumilus</i> .	Kenya/ Africa	Omosa et al. (2014)
Penduletin, anhydrous crystal of penduletin and viscosine	UV, MS, 1D, 2D, NMR spectroscopy	Anti-acetyl- and butyrylcholinesterase activities using spectrophotometric method.	Viscosine exhibited moderate acetylcholinesterase (IC ₅₀ = 182.97 ± 1.25 M) and significant butyrylcholinesterase (IC ₅₀ = 47.07 ± 0.54 M) inhibitory activities. Penduletin (IC ₅₀ = 55.78 ± 1.01 M) and anhydrous crystal of penduletin (IC ₅₀ = 58.72 ± 1.02 M) showed moderate anticholinesterase activity.	Pakistan/ South Asia	Muhammad et al. (2015)
Viscosol	2D, NMR, HREIMS	Protein tyrosine phosphatase 1B inhibitory assay.	Highest PTP1B inhibition was at an IC ₅₀ value of 13.5 μ M.	Pakistan/ South Asia	Uddin et al. (2018)
5,6,8-trihydroxy-7,4'-dimethoxy flavone (TMMC)	UV, IR, NMR spectroscopy	Broth microdilution assay and Biofilm assay.	Anti-proliferation of the growth of <i>Candida albicans</i> was recorded and the MIC and MFC values of 0.39 mg/mL and 1.56 mg/mL were noted. Biofilm inhibition was associated with a concentration of 0.39 mg/mL for the tested extract.	South Africa/ Africa	Patel et al. (2020)

Table 3 continued

Sample type or compound	Identification of compounds and structures	Assays used	Overall results summary and MIC values	Country/Region	References
Flavonols					
Rhamnocitrin	UV, MS, 1D, 2D, NMR spectroscopy	Agar well-diffusion method used for evaluation of antimicrobial activity.	MIC values of 62.5 µg/well and at 125 µg/well slight inhibition against <i>Staphylococcus aureus</i> and <i>Bacillus pumilus</i> were recorded.	Kenya/ Africa	Omosa et al. (2014)
Quercetin-3',7-dimethyl ether	UV, MS, 1D, 2D, NMR spectroscopy	Agar well-diffusion method used for evaluation of antimicrobial activity.	Some inhibition against <i>Escherichia coli</i> and <i>Bacillus pumilus</i> with a MIC value of 31.25 µg/well and at 62.5 µg/well slight inhibition against <i>Staphylococcus aureus</i> .	Kenya/ Africa	Omosa et al. 2014
Flavanones					
5,4'-Dihydroxy-7-methoxyflavanone	UV, MS, 1D, 2D, NMR spectroscopy	Agar well-diffusion method used for evaluation of antimicrobial activity.	Some inhibition against <i>Saccharomyces cerevisiae</i> with a MIC value of 7.8 µg/well and at 125 µg/well slight inhibition against <i>Bacillus pumilus</i> and <i>Staphylococcus aureus</i> .	Kenya/ Africa	Omosa et al. (2014)
3,5,7-trihydroxy-4'-methoxyflavone (1)	NMR analysis	DPPH spectrophotometric (quantitative) assay to test for antioxidant activity and microdilution assay to determine MIC.	Some antioxidant activity. Inhibition of <i>Enterococcus faecalis</i> with a MIC value of 23 µg/well. At 125 µg/well some inhibition against <i>E. coli</i> and at 250 µg/well slight inhibition against <i>Pseudomonas aeruginosa</i> and <i>S. aureus</i> .	South Africa/ Africa	Teffo et al. (2010)
5,7,4'-trihydroxy-3,6-dimethoxyflavone (2)	NMR analysis	DPPH spectrophotometric (quantitative) assay to test for antioxidant activity and microdilution assay to determine MIC.	Some activity against <i>Escherichia coli</i> with a MIC value of 26 µg/well. Reasonable activity against <i>Pseudomonas aeruginosa</i> at 32 µg/well and some activity against <i>Enterococcus faecalis</i> . At 125 µg/well some activity against <i>S. aureus</i> .	South Africa/ Africa	Teffo et al. (2010)
5-hydroxy-3,7,4'-trimethoxyflavone (4)	NMR analysis	DPPH spectrophotometric (quantitative) assay to test for antioxidant activity and microdilution assay to determine MIC.	No activity at 250 µg/well.	South Africa/ Africa	Teffo et al. (2010)
3,4',5,7-tetrahydroxyflavone (5)	NMR analysis	DPPH spectrophotometric (quantitative) assay to test for antioxidant activity and microdilution assay to determine MIC.	Some antioxidant activity and decent antibacterial activity. Had activity against <i>Escherichia coli</i> with a MIC value of 16 µg/well and at 32 µg/well some activity against <i>Enterococcus faecalis</i> . At 63 µg/well had some activity against <i>Pseudomonas aeruginosa</i> and <i>Staphylococcus aureus</i> .	South Africa/ Africa	Teffo et al. 2010
Pinocembrin	UV, MS, 1D, 2D, NMR spectroscopy	Agar well-diffusion method used for evaluation of antimicrobial activity.	Good antifungal activity against <i>Saccharomyces cerevisiae</i> with a MIC value of 31.25 µg/well. Some activity against <i>Staphylococcus aureus</i> at 62.50 µg/well.	Kenya/ Africa	Omosa et al. (2014)

Table 3 continued

Sample type or compound	Identification of compounds and structures	Assays used	Overall results summary and MIC values	Country/Region	References
Terpenoids					
Dodonic acid	UV, MS, 1D, 2D, NMR spectroscopy	Agar well-diffusion method used for evaluation of antimicrobial activity.	Some inhibition activity against <i>Saccharomyces cerevisiae</i> with a MIC value of 62.50. At 250 µg/well some activity against <i>Bacillus pumilus</i> .	Kenya/Africa	Omosa et al. (2014)
2β-hydroxyhardwickic acid	UV, MS, 1D, 2D, NMR spectroscopy	Agar well-diffusion method used for evaluation of antimicrobial activity.	Some inhibition activity against <i>Saccharomyces cerevisiae</i> with a MIC value of 125 µg/well and against <i>Bacillus pumilus</i> and <i>Staphylococcus aureus</i> at 250 µg/well.	Kenya/Africa	Omosa et al. (2014)
Hautriwaic acid lactone	UV, MS, 1D, 2D, NMR spectroscopy	Agar well-diffusion method used for evaluation of antimicrobial activity.	Decent antifungal activity against <i>Saccharomyces cerevisiae</i> with a MIC value of 7.8 µg/well and very poor antibacterial activity.	Kenya/Africa	Omosa et al. (2014)
Hautriwaic acid	UV, MS, 1D, 2D, NMR spectroscopy	Agar well-diffusion method used for evaluation of antimicrobial activity.	Less active against <i>Saccharomyces cerevisiae</i> . Some activity against <i>Bacillus pumilus</i> with a MIC value of 125 µg/well and against <i>Staphylococcus aureus</i> at 250 µg/well. At 500 µg/well there was also some activity against <i>Saccharomyces cerevisiae</i> .	Kenya/Africa	Omosa et al. (2014)
Dodovisnoid A to G	2D, NMR, HRESIMS	In vitro antiviral effect against herpes simplex virus type 1 (HSV-1) using cytopathic effect (CPE) assay.	Compounds D to G exhibited a range of inhibitory activity (IC50 values = 5.5 ± 0.4 to 38.1 ± 3.3 mM).	China/East Asia	Zhang et al. (2016)
15,16-epoxy-neo-clerodan-1,3,13(16),14-tetraen-18,19-olide/ Hardwickiic acid/ Divinatorin A/ ent-15,16-epoxy-1,3,13(16),14-clerodatetraen-18-oic acid	UV, MS, 1D, 2D, NMR spectroscopy	In vitro antiviral activity against H3N2 monitored through the cytopathic effect (CPE) assay.	H3N2 inhibition with IC50 values ranging between 24.8 ± 1.7 µM and 58.1 ± 6.6 µM.	China/East Asia	Zhao et al. (2021)
Dodovisin A and E and stritic acid from <i>D. viscosa</i>	IR, UV, MS, 1D, NMR spectroscopy	The ADP-Glo™ luminescence assay monitoring ACLY activity.	ACLY inhibition with IC50 values ranging between 0.24 ± 0.09 and 3.02 ± 0.53 µM for the three compounds. Positive control (IC50 = 0.26 ± 0.01 µM).	China/East Asia	Lei et al. (2021)

*This list is not necessarily exhaustive

Phenolics

The phenolics have received a lot of attention in terms of human health and *Dodonaea* is now well established to have a range of flavonoids and phenolic acids (Kondratyuk and Pezzuto 2004) (Fig. 6, Table 2 and Table 3). It is clear that the flavonoids represented by flavones, flavanols and flavonols are widespread in different extracts and plants in *Dodonaea*. The flavone scaffold is a phenylchromen-4-one (2-phenyl-1-

benzopyran-4-one) and the molecular formula of the flavone molecule is $C_{15}H_{10}O$. Phenylalanine is vital as a precursor in flavonoid biosynthesis as the production of coumaryl CoA is dependent on the phenylpropanoid metabolism where phenylalanine (from primary metabolic pathways) has a central role (Fraser and Chapple 2011). Condensation, catalyzed by chalcone synthase leads to production of 5,7,4'-trihydroxy-3,6-dimethoxyflavone which has been identified as the major flavonoid of *D. viscosa* var *angustifolia* (Teffo

et al. 2010). The many different isomers of methoxyflavone are especially interesting from the therapeutic point of view as they have been shown to possess significant biological activities (Vue et al. 2016). Some of the flavonoids isolated from *D. viscosa* are reported (see review of Rani et al. (2009) and references therein). These phytochemicals occur in various plant parts including seeds, bark, flowers, flower stalks and leaves at variable levels (Fasola and Iyamah 2014). Qualitative and quantitative differences in flavonoid pools appear to be dependent also on season, and geographic locality where male and female flowers may differ in their chemical constituents (Sati et al. 2013; Soni et al. 2015). The significance of the prenylated flavonoids, rather than the more simple flavonoids, that are ubiquitously abundant in *Dodonaea* is one of the chemotaxonomic features associated with members of the Sapindaceae (Al-Aamri and Hossain 2016). In *D. polyandra* both stems and leaves accumulate flavonoids as a surface residue. Work in this species by Simpson et al. (2011) showed two novel monoprenylated and one diprenylated flavonoids that were exclusively isolated from stem tissues.

The study of Niu et al. (2010) presented four new chemical isolates, identifying two new prenylated flavonoids (namely; 5,7,4'-trihydroxy-3',5'-di(3-

methylbut-2-enyl)-3,6-dimethoxyflavone and 5,7,4'-trihydroxy-3'-(4-hydroxy-3-methylbutyl)-5'-(3-methylbut-2-enyl)-3,6-dimethoxyflavone). Ethyl acetate extraction following a repeated column chromatography approach before HR-ESI-MS was essential in the study. 4',5,7-trihydroxy-3-methoxyflavone (called also isokaempferide) and 3,4',5,7-tetrahydroxy-6-methoxyflavone, found in many other plant species, were reported in *D. viscosa* extracts from Kenyan plants for the first time in 2014 by Omosa et al. In a recent study, a methanol-derived extract was subjected to serial purification using Dianion HP-20, silica gel, octadecyl-functionalized silica gel, and Sephadex LH-20 matrices. This led to a unique flavonol with a long fatty acid tail being isolated, named visconata. This was done through a bioassay-guided structural isolation approach for human neutrophil elastase (HNE) inhibitors associated with inflammation. The flavonol moiety (5,7-dihydroxy-2-(4-hydroxy-3-(4-hydroxy-3-methylbutyl)phenyl)-3,6-dimethoxy-4H-chromen-4-one) bonded to an odd-numbered long chain (C19) fatty acid with fragment ions at m/z 399 [M-327] and 416 [M-310], was used as a diagnostic feature with EI-Mass analysis (Uddin et al. 2017). This structure now referred to as visconata is extremely rare in land plants, confirming the unique chemistry of *D. viscosa*

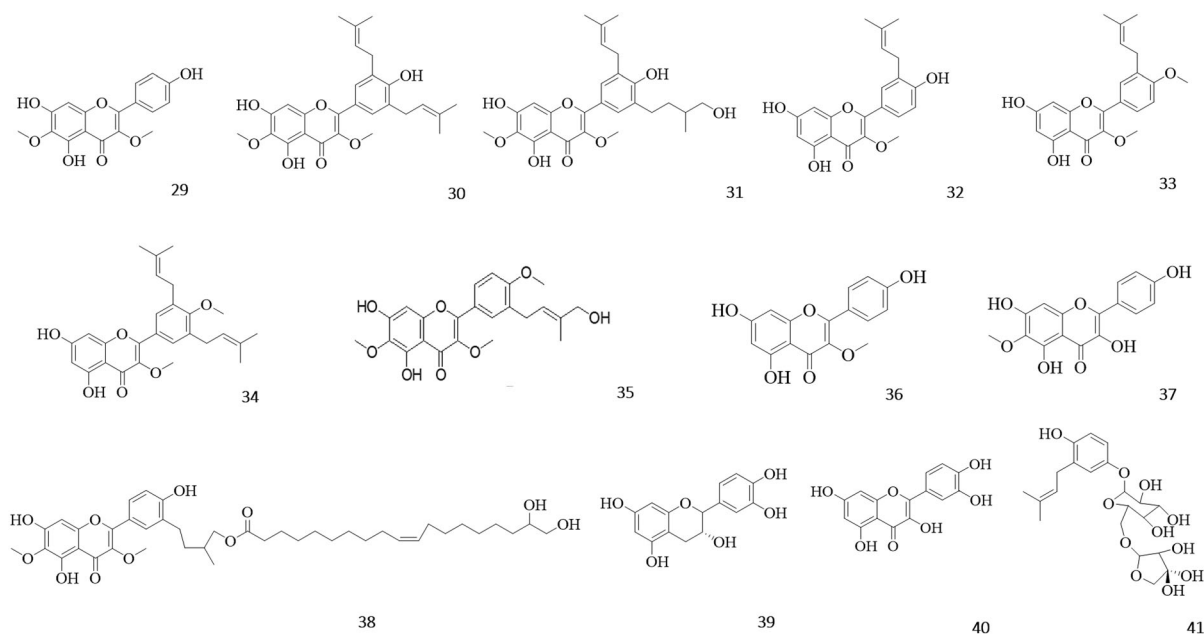


Fig. 6 Chemical structures for some of the new phenolics isolated from different varieties of *Dodonaea* based on literature

for natural products that have remarkable chemical and pharmacological properties. Methylene-bridged bisflavonoids are also considered rare and hence the isolation of such a compound, methylenebissantin, that is a structural isomer of santin is an exciting finding even though this chemical does not exhibit strong activity in antimalarial assays (Muhammad et al. 2012). Through various spectral analyses (^1H and ^{13}C NMR COSY, HMQC and HMBC), its structure was determined to be $\text{C}_{37}\text{H}_{32}\text{O}_{14}$ (HRTOF-ESI-MS; m/z 701.1725). The leaves of *D. viscosa* samples from the Sultanate region of Omar were proven to contain 3,3',4',5,7-pentahydroxyflavane when a hot methanol was used for extraction by Al Habsi and Hossain (2018) in a bioassay-guided isolation of compounds with antioxidant properties. In another set of experiments that included gravitational chromatography and preparative TLC using material from the same region, 5-hydroxy-7,3'4'-trimethoxy-6-acetoxy-3-prenylflavone, a new prenylated flavonoid was isolated from the chloroform extract and the structure determined using 1D (^1H and ^{13}C) and 2D (COSY, HMQC and HMBC) NMR spectroscopy and HRMS (Al-Aamri and Hossain 2016).

Other phytochemicals

A study investigating the effects of pyrolysis of *D. viscosa* leaves using an Indian traditional method of preparation found the main components to be 5-methyl-2-furancarboxaldehyde; 3-methyl-2-cyclopenten-1-one; 3-methoxy-1,2-benzenediol; cresols; substituted mono-, di- and trihydroxybenzenes and; 1,4:3,6-dianhydro- α -glucopyranose when the pyrolysate was subjected to GC-MS. Phenolic compounds made up 50% of the pyrolysate (Shanmugavasan and Ramachandran 2011). The authors were interested in analyzing the chemicals of the crude extract prepared using burning of plant materials in earthen pots as the extract is generally used to treat pain and inflammation, musculoskeletal problems, arthritis, rheumatism and other phlebological and lymphological health issues. A myo-inositol derivate, determined as 1-L-O-methyl-2-acetyl-3-p-cis-coumaryl-myo-inositol ($\text{C}_{18}\text{H}_{22}\text{O}_9$, $[\text{M} - \text{H}]^-$ peak at m/z 381.1143) was purified from ethanol extracts of the leaves by Mostafa et al. (2014). Both the *cis* and *trans* forms were identified in the extracts. As all the parts of the *Dodonaea* plant have

medicinal values, differences in their phytochemical constituents is pretty well acknowledged (Anilreddy 2009). There are several pioneer studies that have showed qualitative differences in the phytochemical constituents of different plant parts. In a recent study 6-hydroxykaempferol-3,6-dimethylether-4'-O-glucopyranoside was isolated from the flowers of the plant, a plant part used to brew a bitter tonic in folklore (Shafek et al. 2015). To produce this tonic in the laboratory, 80% ethanol was used for the extraction followed by chromatography on a polyamide column.

Biological activities

There is a considerable amount of literature on the pharmacology of single chemical isolates, fractions and complex extracts obtained from *D. viscosa*. Alcoholic extracts produced with ethanol or methanol are amongst the most popular for study against a variety of diseases and these studies are well aligned with the way the plant is used in various countries as a traditional medicine (Table 3). In the sections that follow, studies to examine the bioactivity of crude extracts and purified compounds isolated from *Dodonaea* species are presented.

In vitro studies

The antimicrobial activity of flavonoids was said to be dependent on the presence of free hydroxy groups which are involved in hydrogen bonding with biological material (Cushnie and Lamb 2005). The position of hydroxyl groups on the flavone backbone often determines the extent of antimicrobial activity of a particular compound (Sarbu et al. 2019). As *D. viscosa* plants have a considerable array of flavonoids with free hydroxyl group(s) it is expected that these extracts would exhibit antimicrobial activity. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) using the microtitre plate assays are more reliable than some of the qualitative antimicrobial assays where the inhibition zone of the extract (eg. disc diffusion assay) is measured (Parvekar et al. 2020). One of the most thorough studies on the antimicrobial activity of extracts prepared from *D. viscosa* is that by Getie et al. (2003) and this work included analysis for microbial activity on several different organisms: 1) antibacterial activity [*E. coli* (ATCC No. 25922), *S. aureus* (ATCC No. 29213), *P.*

aeruginosa (ATCC No. 27853) and *Corynebacterium diphtheriae* (ATCC 11051)]; 2) several clinical fungal isolates (*S. pyogenes*, *C. albicans*, *Aspergillus fumigatus* and *Trichophyton rubrum*), and 3) antiviral activity [using the viral strains including Coxsackie virus B3 (CVB3) strain and Influenza A virus] as well as anti-inflammation assays. Some tests were also performed using the green monkey kidney (GMK) and Madin–Darby canine kidney (MDCK) murine macrophage cell lines. Dose-dependent effects of the 80% ethanol extract was shown in human cervix carcinoma cells (HeLa cell line) (CC_{50} value of 96.17 ± 13.86) and on murine macrophage cells, the CC_{50} was recorded as 45 ± 3.5 μ g/ml. Ethanolic extract was found to be a promising extract screened by Heyman et al. (2009) for antibacterial activity using the MIC and MBC methods (MIC = 500 μ g/ml for an ethanol extract against a *Staphylococcus aureus* methicillin-sensitive strain (ATCC 12600)). In the same study, cytotoxicity analysis of the same extract was measured using Vero African green monkey kidney cells (ATCC CCL-81) in a XTT Cell proliferation assay to record an IC_{50} of 42.11 μ g/ml.

Omosa et al. (2014) tested both crude extracts and 14 compound isolates from *D. angustifolia* using the agar well-diffusion method to determine the MICs against Gram-negative (*Escherichia coli*), Gram-positive (*Staphylococcus aureus* and *Bacillus pumilus*) bacteria and *Sacchromyces cerevisiae*, a yeast. These extracts were generated from different populations in Kenya and differences in antimicrobial activity was prevalent due to the chemotypic profiles of the extracts being variable. Strong antifungal effects were noted for the compounds, hautriwaic acid lactone and santin and this was ascribed to the lipophilic nature of the chemicals tested. The extracts tested in that study also showed other antimicrobial effects. According to Zhang et al. (2016), dodovisnoids A to G were tested for their effect against herpes simplex virus type 1 (HSV-1). Dodovisnoid A and B were inactive in vitro using cytopathic effect (CPE) assay, whereas dodovisnoid D to G all showed considerable activity. Other earlier studies showing antiviral actions of extracts and purified compounds are those from De Oliveira et al. (2012) where the selectivity index ($SI = CC_{50}/IC_{50}$) was determined to be 6.2 in vitro for the crude extract. None of the fractions or pure compounds had better activity compared to the whole extract suggesting a chemical synergism that may be at play that leads

to antiviral effects of the phytoextract (Ryabushkina 2005). In another study, *Aspergillus niger*, *A. flavus*, *Microsporum gypseum*, *Trichophyton rubrum* and *Paecilomyces varioti*, were the batch of test organisms and out of the extracts produced using ethanol, methanol, ethylacetate, chloroform and water, the chloroform extract showed the best antifungal inhibition (Pirzada et al. 2010) for skin related diseases. Various in vitro studies focusing on anti-inflammation have shown that the labdane diterpenoids of *D. viscosa* possess pronounced anti-inflammatory effects such as the study by Wabo et al. (2012) where the TNF-alpha-secretion capillary flow cytometry assay was conducted. Inflammation in animal bodies is a complex response involving various mediators (TNF-alpha, IL-1beta, phospholipase A2, nitric oxide, COX-1 and COX-2, and lipoxygenase enzymes) apart from other molecular mechanisms. Products that are able to interact with these mediators are thus important in regulating inflammation (Kumar et al. 2019b).

Human neutrophil elastase (HNE) inhibition is an important marker for those products that have potential in treating respiratory problems and/or acute lung injury, obstructive chronic pulmonary ailments, atherosclerosis, cystic fibrosis, and rheumatoid arthritis (Crocetti et al. 2019). Visconata, a rare flavonol fatty acid, showed anti-HNE effects. As expected this effect was dosage dependent and an IC_{50} value of 2.4 μ M was recorded (Uddin et al. 2017).

Plants that show a diversity in their flavonoid profiles become very interesting for experiments investigating antioxidant and anticholinesterase activities (Zafar et al. 2019). A batch of tests to calculate IC_{50} values for using various in vitro assays: β -carotene-linoleic acid for lipid peroxidation, 1-diphenyl-2-picryl-hydrazyl (DPPH) free radical, ABTS cation radical, superoxide anion radical scavenging, metal chelating, and CUPRAC assays were important in the work of Muhammad et al. (2015). This study tested 12 *D. viscosa* flavonoid biomarkers as structure–activity relationships (SAR) strongly influence antioxidant potential of plant derived extracts. The authors concluded that some of the chemicals were more suited as antioxidants, but others exhibited stronger anticholinesterase activity than galanthamine that was used as a positive control in the BChE enzyme inhibitory activity test. Several other studies have focused on antioxidant effects of *D. viscosa* extracts using the DPPH assay (Table 3). Hexane extracts were

said to have high antioxidant properties (94.41 ± 0.12 percentage inhibition in the DPPH assay) in a study by Al Habsi and Hossain (2018) where the least inhibition was detected for a butanol extract. As part of this work, the characterization of the pure compounds in terms of the antioxidant effects showed that 3,3',4',5,7-pentahydroxyflavane was more active than 4-methoxystigmasterol.

African traditional medicine uses the concept of synergism often for producing polyherbal mixtures that are effective against various ailments (Malongane et al. 2017). The idea of combining different plant species leads to a highly complicated chemistry that is extremely pharmacologically active and prevents the development of resistance in for example microbial organisms (Efferth and Koch 2011). Zonyane et al. (2013) tested a plant herbal remedy that contains *D. viscosa* for antimicrobial activity. The inclusion of *D. viscosa* contributed to additive and synergistic effects that made the extract that also had *Agathosma betulina* and *Eucalyptus globulus* more potent compared to other mixtures tested in that study. Nanoparticle technology is a highly innovative means of delivery of therapeutic drugs. Therefore, the study of Anandan et al. (2019) used silver nanoparticles from water and acetone extracts of *D. viscosa* to test the effect of this technology in improving the antibacterial and anti-cancer effects. However, the normal extracts were more effective in their bioactivity compared to the nanoparticles. Another study that is noteworthy of mentioning is that of Naidoo et al. (2012) which studied the effect of the *D. viscosa* var *angustifolia* extract on the formation of a biofilm linked to the oral pathogen *Streptococcus mutans* when sublethal concentrations of the extract were applied in vitro. High levels of catechin or chromene derivatives, various chalcones with trimethoxyphenyl group and 4-O- β -D-xylopyranoside were analyzed. It was clear that many of the compounds possess antibacterial effects, hence, reductions in the presence of *S. mutans* in vitro. This study is followed by another one where the flavone isolated from *D. viscosa*, namely 5,6,8-trihydroxy-7-methoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (TMMC) was tested for its effects against biofilm formation in an attempt to prevent dental cariogenesis (Ngabaza et al. 2018). Both the extract and the pure compound showed positive inhibition of bacterial growth. The colonization of epithelial tissues by *C. albicans* requires several steps that initiate the

infection process in mammalian cells prior to the formation of a biofilm and production of polymeric matrices generated by the yeast, preventing fungicidal and fungistatic chemical agents from entering the yeast cells that have the potential to reduce fungal growth (Gow et al. 2012). An in vitro study coupled electron microscopy to monitor the morphology of the fungus in the presence of a *D. viscosa* extract generated from plants growing in South Africa (Naicker and Patel 2013). Of interest was the decrease in percentages of germ tube formation when the extract was supplied at 3.125, 1.56, and 0.78 mg/ml and the frequency of the germ tube production was reduced by 85.36, 61.91, and 26.27%, respectively. Scanning electron microscopy further showed a lowered amount of biofilm formation and fewer hyphae being present when the extract was in contact with the *Candida* cells.

The phytochemical interest on *D. viscosa* has not only been for the human or veterinary pharmaceutical uses, but also on identification of those compounds that may inhibit growth of plant pathogens that cause major losses in the cultivation of agricultural plant crops. As an example the study of El-Gengaihi et al. (2011) is appropriate as two flavonoids: quercetin 3-O-glucose 7-O-rhamnoside and quercetin 3-O arabinose 7-O rhamnoside that were subsequently analyzed for their effects on the spider mites, *Tetranychus urticae*. The most effective extract was the ethanol extract, but butanol extract which was used to obtain saponins also exhibited good acaricidal activity. The authors reported a 90% mortality rate in the insects' post hatching for the ethanol extract, while the saponin-containing extract led to only 20% mortality of the mites during experimentation. The bioactivity studies in vitro focusing on antibacterial effects of various *D. viscosa* extracts attest to the inhibitory potency of the extracts on various micro-organisms. The emergence of multi-drug resistant bacterial strains is one of the key incentives for the search of new bioactive ingredients that combat this problem (Cheesman et al. 2017). 5,6,8-trihydroxy-7-methoxy-2-(4-methoxyphenyl)-4H-chromen-4-one, isolated by Ngabaza et al. (2017), using a bioassay guided approach, from the methanol extract of dried leaves of *D. viscosa* is one example that focused on antimicrobial effects of the species. In many cases, ethanol and methanol are often used as the extractant and MIC values using a microplate dilution assay are generated.

Phenolics and terpenoids are known to show antiproliferative effects on cancer cell lines and they remain powerful agents that can be developed to therapeutic drugs to restrict neoplastic diseases (Roy et al. 2018). With the aim to provide structure–activity relationships of the isolates: 5,4'-dihydroxy-7-methoxyflavanone; 5,7,4'-trihydroxy-3',5'-diprenylflavanone; hautriwaic acid; 2 β -hydroxyhardwickiic acid; and hautriwaic acid lactone using A549 human non-small cell lung cancer; PC212 human mesothelioma and Caco-2 colorectal adenocarcinoma plus a normal skin fibroblasts cell line (CRL2120), the study of Kuete et al. (2019) provided a comprehensive analysis using a battery of different tests such as the neutral red uptake assay, cell cycle analysis and detection of apoptosis via flow cytometry, the caspase assay, mitochondrial membrane potential and ROS analysis (OxiSelect™ Intracellular ROS Assay Kit). Although out of the compounds tested none were as active as Doxorubicin, the 5,4'-dihydroxy-7-methoxyflavanone was amongst those that had the best activity (IC₅₀ of 5.98 $\pm$ 0.48 μ M and a selectivity index of 5.63). It is noteworthy to mention that prenylation of this flavanone, led to lowering of activity against the breast adenocarcinoma MCF-7 cells (Kuete et al. 2018). The root extracts of *D. viscosa* from Madagascar are a source of dodoneasides A and B, oleanane-type triterpene saponins that can be extracted with dichloromethane. These chemicals show considerable anticancer activity (IC₅₀ values of 0.79 and 0.70 μ M, respectively) when applied to A2780 human ovarian cancer cells (Cao et al. 2009).

In vivo studies

Some of the early studies, conducted in the late 1990s and reports published from 2000 onwards on *D. viscosa* showed effects of extracts in animal models (Rani et al. 2009). The study of Khalil et al. (2006) provides a good example here where evidence of anti-inflammatory effects using rats for an ethanol extract was concluded. Other studies have since this time followed including clinical fungal isolates obtained from HIV-infected human patients, however, using an in vitro assay (the study of Patel and Coogan (2008) and (Patel et al. 2009) refers). This latter study uses an oral epithelial cell line to test the effectiveness of the extract on preventing adhesion of *Candida albicans* to the cell line in vitro with the aim to test this in a clinical

trial setting. In certain parts of India, particularly in the Tamil region, the use of *D. viscosa* for gastric diseases is prevalent (Sankaranarayanan et al. 2010). A study using both female and male Charles Wistar rats (120–160 g) focused on determining the effects of different extracts on the gastric diseases and various blood-related indicators linked to haematological and serum biochemical parameters (including aspartate aminotransferase, alanine aminotransferase, creatinine, hemoglobin, triglycerides, and urea) were also measured (Arun and Asha 2008). Out of the extracts tested, the hexane extract offered the best gastroprotective effects, preventing gastric ulcer aggravation in the test animals. In another study, also using rats, hepatoprotection was defined through lowered ROS generation in hepatocytes with fewer inflammatory and cytotoxicity mediators being detected from CD68 + macrophages and hautriwaic acid was prominent in HPLC chromatograms of different extracts. This particular chemical has well established anti-inflammatory effects (Ali et al. 2014). Analgesic and antipyretic activities of a water extract of *D. viscosa* var. *angustifolia* was evident in a study that used mice in the hotplate and antipyretic activity tests. In other animal studies, pre-diabetic mice exhibited signs of hyperglycemia, hypertriglyceridemia and hyperinsulinemia (Veerapur et al. 2010a, b, 2010a). This study appears to be thorough as several parameters were monitored. Apart from an in vitro analysis of Protein tyrosine phosphatase-1B [PTP-1B] inhibition assay, PPAR γ -ligand binding domain assay and the Dipeptidyl peptidase-IV (DPP-IV) inhibition assay, blood sample analysis of the mice on various extracts and fractionated extracts were monitored for blood glucose, serum insulin and HOMA levels as well as lipid biomarker indicators were analyzed.

Some studies have looked at the bioactivity of isolated compounds and the flavonoids have been studied in greater detail compared to other chemicals. Simpson et al. (2014), using an in vivo mouse model, examined three clerodane diterpenoid isolates for their anti-inflammation effects in a TPA-induced mouse ear edema model as part of a strategy to find new drugs to alleviate skin inflammation diseases. Dosage was important in the effect in animals with one of the compounds (polyandric acid A) exhibiting significant activity at a 30 μ M concentration. The compounds tested were originally obtained from *D. polyandra*. The flavonoid viscosine was examined for its

lipoxygenase inhibitory activity using molecular docking with the assay IC₅₀ value of this compound determined to be $39.4 \pm 0.2 \mu\text{M}$ (Khan et al. 2013). Computational molecular docking analysis revealed the importance of the C7 part of bicyclic aromatic viscosine as being the region on the chemical ring structure that was critical for hydrogen bonding with the Ile857 and His523 sections of the catalytic site of the lipoxygenase enzyme, providing new insights on the biochemical mechanism that renders this enzyme inactive.

Lipoxygenase is implicated in several diseases where inflammation occurs and chemicals that interfere with its catalytic activity are thus implicated in controlling diseases where inflammation is linked to the pathology. Diseases caused by parasites, such as *Plasmodium* leading to malaria, are a major burden on the health system in countries where infections prevail (Autino et al. 2012), hence, the search for therapeutics that can manage disease or control the levels of infection before the manifestation of disease symptoms (Kumar et al. 2019a). In the in vivo study of Melaku et al. (2017), *Plasmodium berghei* and male Swiss albino mice were used in the antimalarial assay. Various pure compounds, fractions were tested for their effects on disease progression in the test animals using Peter's 4 day suppressive examination. At a dose of 300 mg/kg, the ethanol leaf extract reduced the amount of parasites by 77.2% and out of the fractions tested (Table 3); the hexane and ethyl acetate fractions were effective in reducing parasitemia. Two flavones, 5,7,4'-trihydroxy-3,6-dimethoxyflavone and 5,6,7-trihydroxy-3,4'-dimethoxyflavone, exhibited superior bioactivity in vivo but the clerodane diterpene, 2-hydroxy-15,16-epoxyceloda-3,13(16),14-trien-18-oic acid, also exhibited excellent bioactivity, reductions of 70.81% at a dose of 40 mg/kg were noted.

Samples of *D. viscosa* from the Saudi Arabia region were tested for neuroprotective actions using a rat model. This study showed that significant improvements to ischaemic stroke in the animals were linked to several bioactives that have antioxidant effects that are constituents of *D. viscosa*. Chemical isolates from ethanolic extracts (Viscomarfadol, isorhamnetin-3-O-rutinoside and procyanidin B1) were responsible for the pharmacological activity. Viscomarfadol was isolated from *D. viscosa* for the first time (Almarfadi et al. 2024).

More work in understanding the effects of *Dodonaea* extracts using animal models are urgently needed and this would benefit clinical studies that may be important in characterizing the physiological effects of extracts of plants from this genus in humans.

General and future perspectives

To our knowledge, there are currently no standardized extracts of *D. viscosa* that are commercially available despite the significance of this plant in traditional medicine that is common throughout the regions where it is found. Even though the study of Pengelly (2008) was thorough in its analysis of *D. viscosa* extracts for developing a topical formulation that could be applied for dermatitis and arthritis as part of the Essential Oils and Plant Extracts R&D program of the Rural Industries Research and Development Corporation (Australia), no commercialized extract was generated from this work. A standardized formulation based on one or some of the *Dodonaea* species or at least including *D. viscosa* as a botanical ingredient seems plausible. There are several different criteria that need to be met in order to guarantee a quality product as consistency and constancy of the composition is critical. This is a prerequisite step that will assist with a reliable clinical analysis using human trials.

There are thus several challenges at present. Basic information is still missing as the therapeutic active ingredients that are reliable biomarkers for such an extract are still not very clear for the diverse range of ailments that these plants are used for. For example; biogeographic influences to the chemical profile of medicinal plants pose unpredictable chemical composition as both qualitative and quantitative differences in the key compounds are altered. The relationship between different populations and effectiveness in both in vitro and in vivo pharmacological tests becomes a problem identified with the species. Out of the studied extract types, those made from alcoholic solvents are dominant in the primary literature, but the mode of preparation has not yet been standardized. The literature survey demonstrates the structural characterization of some of the phytochemicals present in *Dodonaea* extracts but there are still many unknown specialised metabolites where isolation, purification and identification are urgently needed. A concerted effort to fill the knowledge gaps in this

regard is an important future consideration. The bioactivities of key ingredients responsible for the reported pharmacological effectiveness of extracts still remains poorly resolved and have not been adequately studied. A patent indicates differences in activity against a breast cancer cell line when plants of *D. viscosa* var *angustifolia* were obtained from three different geographical localities (refer to Makunga and Engelbrecht 2019). To ensure a consistent phytochemical profile, harvesting times and post-harvest processes are required for the species. Otherwise, inconsistencies lead to unknown toxicology and efficacy of extracts and safety aspects are thereby compromised. To this end, agricultural field cultivation is one way towards uniformity of a plant extract, minimizing biochemical variation, most especially if clonal materials are used. Baruch et al. (2018) show strong intraspecific variation in ecophysiological function in *D. viscosa* distributed in parts of Australia. In such cases, metabolomic profiles are likely to vary and the work conducted as part of our research shows variation in both phenolic and flavonoid content in extracts from plants collected from different environments in South Africa and Kenya (Kaigongi et al. 2020). Chemotype selection for elite populations that have superior bioactivity will thus be critical for future studies that aim at quality assured extracts for industrial applications. At present it is unknown whether the chemotype variability is linked to environmental induced phenotypic plasticity and/or inherent genetic population structure. The impact of abiotic and biotic stresses on the phytochemistry of *Dodonaea* has yet to be investigated. Such studies would be more meaningful if a reference genome becomes more available for these plants as molecular biological insights into the regulator mechanisms that govern the biosynthesis of the phytochemicals is explored in the future. The combination of advancements in modern genomics and metabolomics tools offers a powerful analytical strategy to add new and deep scientific information that can provide further clarity on the taxonomic and evolutionary relatedness of species, subspecies and variants in the genus *Dodonaea*. Future research endeavours should thus exploit the rapidly developing technologies linked to next-generation sequencing and metabolite profiling, respectively. Further studies associated with understanding of structural activity relationships, toxicology and safety, herb-drug interactions, pharmacodynamics and

pharmacokinetics in both preclinical and clinical settings, impacts of dosage in relation to short-term and long-term use for reasonable development of the use of chemical isolates and extracts generated from *Dodonaea* plants are important for modern pharmaceutical applications. There is a general lack of empirical data pertaining to molecular biological mechanisms of phytoextracts using in vitro and in vivo pharmacological models. This information would thus provide added evidence to support the medicinal potential that can ultimately lead to the commercialization of *Dodonaea viscosa* and related sister species.

Conclusions and recommendations

This review highlighted the remarkable natural products that are synthesized by different *Dodonaea* species and the increasing amount of phytochemical and pharmacological information that has been published in recent years, especially related to *D. viscosa* and its variants. This study has thus shown that the genus *Dodonaea* is an important source of rare compounds in nature and recently characterized compounds represent new chemical entities that have not previously been reported, illuminating real possibilities in future bioprospecting endeavours that are geared towards commercialization of extracts of *D. viscosa* or those compounds that are derived from this species as a likelihood. Although many studies with aim of drug discovery are testing the single isolates in in vitro assays, the number of in vivo studies although limited to complex crude extracts, and or fractionated extracts, have increased in the recent past. Some studies highlight (Kaigongi et al. 2020) the need to better profile naturally occurring populations for novel compounds and to define the chemical constituents of different chemotypic profiles. With the adoption of metabolomics for the biogeographical delineation of *D. viscosa* chemotypes and sets a foundation for future studies that will assist with the phylogenetic and taxonomic differentiation of species and subspecies of *Dodonaea*. As standardized extracts are not available at all, this creates a bottleneck for products to enter into the phytopharmaceutical markets. Clinical research that better ascertain the safety and toxicity profiles of extracts of standardized extracts of *D. viscosa* and their associated specialized metabolites is

also urgently needed. Resource management is also required to ensure a sustainable supply of plant materials without necessarily endangering wild populations as currently materials for the traditional medicines market are wild harvested.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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