Heliyon 9 (2023) e17081

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Medicinal plants of Jordan: Scoping review

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ARTICLE INFO

Keywords:
Jordan
Medical plants
Phytochemicals
Cancer
Diabetes
Antimicrobial

ABSTRACT

Jordan is rich in the flora of ethnobotanical importance. This scoping review aims to highlight the ethnopharmacological value of Jordanian medicinal plants using the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) guidelines. A total of one hundred twenty-four articles published between 2000 and 2022 obtained from PubMed, EBSCO, and Google Scholar databases were included in this review. These plants own several classes of secondary bioactive metabolites, including alkaloids, flavonoids, phenolics, and terpenes. Jordanian plants exhibited potential therapeutic activity against various tumors, bacterial infections, elevated blood glucose levels, hyperlipidemia, platelets aggregation disorders, and gastrointestinal disorders. Phytochemicals' biological activities depend on their structures, parts used, methods of extraction, and evaluation model. In conclusion, this review highlights the need of researching Jordan's abundant naturally occurring medicinal plants and their phytochemicals as novel lead molecules in drug discovery and development. Studying active phytochemicals for disease treatment will help develop drugs for safe treatment and cure in the future.

1. Introduction

The use of plants and herbs as medicine has increased remarkably worldwide. Many people use these preparations and products to treat various health-related challenges, needs, and illnesses across different countries. Literature also reported that around 80% of the Arab population uses herbal medicine in treating and preventing disorders [1].

Jordan is a Middle Eastern, Arab country with a landscape divided into six biogeographic regions: Mediterranean, Mediterranean-Irano-Turanian, Saharo Arabian, Irano-Turanian, Sudanian, and Saharo-Arabian, bridging between Asia, Africa, and Europe. Consequently, this environmental landscape diversity has influenced the natural habitats and plant flora biodiversity [2–4]. The Jordanian culture is known for its rich heritage of folk medicine, which is common under-researched practice [5]. Ajloune, Jordan, for instance, a well-known city for its heritage of plants due to climatic and fertile soil, exhibits the highest use value of medicinal herbs and plants in treating digestive and dental illnesses. Studies have demonstrated that Jordanians tend to use phytomedicines mostly as self-medication for treating diabetes, dyslipidemia, hypertension, and cancer and in fertility [6]. The availability of plants, the presence of modern medical facilities, and the culture of the society in the region all affect the utilization of plants and herbs for

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https://doi.org/10.1016/j.heliyon.2023.e17081
Received 20 January 2023; Received in revised form 6 June 2023; Accepted 7 June 2023
Available online 7 June 2023

medicinal purposes. Inherently, various concerns were also underlined regarding the use of herbs as medicines, these herbs' efficacy, potential side effects, and herb-drug interaction [7].

It was reported that around 80% of the population in Arab culture use herbal medicine to treat and prevent disease. The Jordanian culture is rich in the precious heritage of folk medicine which is a common under-researched practice. Jordanian have used phyto-medicines mostly as a self-medication for treatment of diabetes, dyslipidemia, hypertension, caner and in fertility [8]. Table 1 shows the ethnobotanical use of herbs in Jordan.

Furthermore, Jordan has rich flora expressed in a variety of plant species. It was reported that Jordan has about 2543 species belonging to 142 different families and 868 genera [7]. Table 1 presents famous Jordanian flora in addition to their traditional uses. This calls for more structured research regarding these diverse species, as this might open new doors for research on Jordanian phytochemicals. It might also shed light on some under-researched domains pertaining to Jordanian flora. Therefore, this review investigates Jordanian plants and herbs' traditional uses and the phytochemical content by describing the ethnopharmacological use, biological activity, secondary metabolite, and mechanisms of action of phytochemicals when applicable. Aiming to examine and explore the literature to report the biological activities of Jordanian herbs to construct an evidence-based medicine for the Jordanian plant species.

2. Method

A scoping review was found to be appropriate to meet the aims of this study as it represents an overview of Jordan's medicinal plants and their utilization. Using the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) guidelines, an extensive search of Scopus, PubMed, and EBSCO. A separate Google Scholar search was conducted in an effort to locate supplementary articles. In addition, hand-searched literature articles were also included to investigate all current relevant studies comprehensively in order to achieve an in-depth exploration of all current relevant studies in this field. Only articles that followed a standardized structure of introduction, method, results, and discussion (IMRAD) were included. The search was narrowed to only include academic articles published from January 2000 to January 2022 (the time of executing this review). Moreover, the studies included in this review must have specifically stated that the plant materials studied have been cultivated and collected from Jordan. Articles included in this review were then critically scrutinized and qualitatively classified into emerging themes with the support of NVivo software V10.

3. Results and discussion

The search initially yielded 3000 articles, which were sorted according to the inclusion criteria mentioned earlier. Articles were then screened by the phytochemical researcher to determine relevance (148 articles). The final selection of articles was concluded by two independent researchers and validated by the research team. The full-text 124 relevant articles that met all inclusion criteria were then analyzed, as shown in Fig. 1.

3.1. Medicinal plants with anticancer activity

Cancer is the leading cause of death [18]. Flowing after heart disease, cancer is the major cause of mortality among the Jordanian population (https://www.cdc.gov/globalhealth/countries/jordan/default.htm). Cancer is a complex disease characterized by the uncontrolled proliferation of cells. Conventional treatments have several side effects and limitations. Therefore researchers have screened a number of medicinal plants for anticancer activities [19,20].

Table 1
Ethnobotanical use of some Jordanian plant species.

Plant Name	Traditional use	Reference	Plant name	Traditional use	Reference
Achillea santolina L	Antispasmodic, diabetes Carminative, depurative stomachaches.	[9,10]	*Pistacia atlantica* Boiss	Edible	[11]
Chrysanthemum coronarium L.	Abdominal pain	[12]	*Pistacia palaestina* Boiss.	Antispasmodic	[12]
Ducrosia flabellifolia Boiss.	Analgesic, cold, antianxiety, antimicrobial	[13]	*Salvia triloba* L.f.	Spasm, carminative, common cold, enhance memory, antidandruff	[12]
Inula viscosa L. Ait.	Anthelmintic, lung disorder, muscle relaxant	[9,10]	*Salvia ceratophylla* L.	Abdominal pain, cancer headaches, coughs stomachaches, asthma microbial infections, and other pulmonary and urinary disorders	[14]
Laurus nobilis L.	Cancer, skin disease	[15]	*Salvia syriaca* L.	infectious diseases and stomach disorders as well as the common cold	[16]
Mandragora autumnalis Bertol.	Sedative, and cough	[12]	*Silybum marianum* L	Liver disease	[9]
Origanum syriacum L.	Abdominal pain, aperative, carminative, cough	[12]	*Tamarix aphylla* L.H.Karst.	Fever	[15]
Ocimum basilicum L.	depression, migraine, cardiac tonic	[9]	*Viscum cruciatum* Sieb	Cancer	[17]

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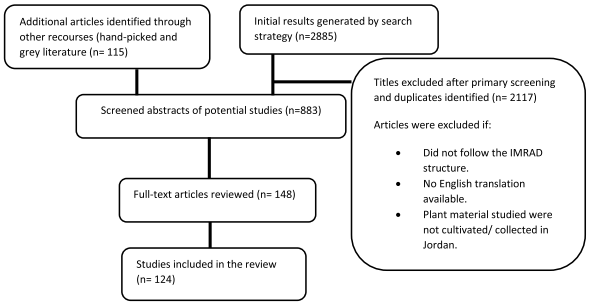

Fig. 1. Flowchart of search strategy and study selection based on PRISMA guidelines.

Cancer is one of the top diseases leading to death after cardiovascular diseases. Plants - derived natural products are constantly take the attention as a promising source to develop new anticancer therapies with more selectivity with no or few serious adverse effects. Cancer hallmarks are biological capabilities acquired by cancer cells during neoplastic transformation. Targeting multiple cancer hallmarks is a promising strategy to treat cancer. The majority of Jordanian plants have a capacity to target the hallmarks of cancerous cells [21].

As shown in Table 2, 41% of tested plant extracts were from leaves, 31% were from aerial parts, and 8% were fruits. Ethanol was the most common extraction solvent (47%), followed by water (13%). It was also found that the human breast adenocarcinoma cell line (MCF-7 cell) was the most targeted by several extracts. The principal method used as an indicator of cell viability, proliferation, and cytotoxicity was the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide assay (MTT assay) followed by the brine shrimp lethality test and sulphorhodamine B assay [4,22].

On the other hand, the most active plant against breast cancer cell line MCF-7 was *Tamarix aphylla* with an IC_{50} of 2.2 μg/mL. *Inula graveolens* (IC_{50} of 3.80 μg/mL), *Salvia dominica* (IC_{50} of 5.80 μg/mL) and *Origanum syriacum* (IC_{50} of 6.4 μg/mL) exhibited also potent and promising antiproliferative activities on a breast cancer cell line (MCF-7).

Tamarix aphylla is s known 'Athel' in Jordan, belongs to family Tamaricaceae. Different parts of the plants are used traditionally for wounds, abscess, headache, fever, skin diseases and for rheumatism and joint pain. Several phytochemicals had been identified; alkaloids, flavonoids, phenolics, tannins and terpenes [23]. In the study of Alhourani both the aqueous and ethanol extracts showed promising cytotoxic activity against MCF-7 cells comparable to cisplatin and with safety even higher than cisplatin against fibroblast (aqueous extract IC50: 80 μg/mL, cisplatin: 9.1 μg/mL) [24].

Inula gravelones is known as stinkwort within the sunflower family. The ethanol extract induced a highly pronounced augmentation of MCF7-caspase-8. The antiproliferative is related to its phytocomponents quercetin and luteolin [25].

Salvia sp is used widely in the Jordanian traditional medicine for common cold, infectious disease and stomach disorders. *Salvia dominica* ethanol extract was biologically active against MCF7 via proapoptotic cytotoxic mechanisms specifically regulated by p21 [26].

The following researches studied the anticancer activity of an isolated compound. In one study, two Jordanian *Colchicum* species of *Colchicum hierosolymitanum* and *Colchicum tunicatum* were fractionated, and several compounds were isolated guided by the brine shrimp lethality test. The colchicine type, the 3-demethyl -colchicine type, and the cornigerine compound were cytotoxic on the same magnitude as the positive control, camptothecin (IC50 values of 3.7–7.7 mg/mL) against MCF-7 human breast carcinoma, NCI–H460 human large cell lung carcinoma, and SF-268 human astrocytoma [4]. Refer to Fig. 2 for the structure of colchicine and cornigerine.

Four flavonoids isolated from Jordanian *Inula viscosa* exhibited high antiproliferative activity against different cell lines (MCF-7 human breast carcinoma, NCI–H460 human large cell lung carcinoma, and SF-268 human astrocytoma). These flavonoids are hispidulin, 3-O-methylquercetin, 3,3′-di-O-methylquercetin, and nepetin [27]. Refer to Fig. 2 for the structure of hispidulin and neptine.

Seven withanolides were isolated from the ethanolic extract of the leaves of *Withania obtusifolia*, namely obtusifonolide, sitoindoside IX, 6a-chloro-5b-hydroxy withaferin A, isowithanone, 2,3-dihydro-3-ethoxywithaferin A, daturataturin A, and withaferin A. The latter compound had the most potent IC50 against the MDA-MB-435 (melanoma) and SW-620 (colon) cell lines [28,29]. Finally, only one isoflavonoid compound isolated from *Gynandriris sisyrinchium* was cytotoxic against the human promyelocytic leukemia HL-60 cells (40 μM) [30]. It is well known that plant extracts contain several secondary metabolites of different classes, like; alkaloids, flavonoids, terpenes, saponins, and volatile oil, that act synergistically and in combination to promote anticancer activity [13].

Different mechanistic pathways discuss the extract's anticancer activity, which includes activation of natural killer cells (NK), which play an essential role in the immune defense against cancer cells, inducing apoptosis as revealed by DNA fragmentation, nuclear condensation, and the formation of apoptotic bodies in treated cancer cells [13,31]. Ability to enhance the secretion of TNF-α (tumor necrosis factor-alpha) and IL-1β (interleukin 1β) and inhibit the release of IL-8 [32,33]. Direct and indirect antiangiogenic properties may have chemotherapeutic and/or chemoprevention potentials. The direct antiangiogenic activity was recognized using the rat aortic assay, anti-HUVEC (human umbilical vein endothelial cells) proliferation, migration, and CAM assay (Chorioallantoic Membrane Assay). The indirect antiangiogenic activity was verified by assessing the effect on VEGF (Vascular endothelial growth factor) and

Table 2
Medicinal plants with anticancer activity.

Plant species	Family	Vernacular name	Part used	Method/Solvent of extraction	Study design	Result	Reference
Achillea santolina L.	Asteraceae	Kaisoom	Aerial parts	Hydrodistillation/ Ethanol	*In vitro* model (MCF-7)	IC_{50} : 24.12 (MCF-7)	[38]
Chrysanthemum coronarium L.	Asteraceae	Besbas or Bassoum	Aerial parts	Maceration/ Methanol	*In vitro* model (T47D)	IC_{50}: 22.6 (T47D) It might be a potential source of natural compounds that can be developed into new antineoplastic agents	[39]
Ducrosia flabellifolia Boiss.	Apiaceae	AlHaza	Aerial parts	Maceration/Ethanol	*In vitro* model (MCF-7, Hep-2, Vero)	IC_{50}: 25.34 (MCF-7), 98.0 (Hep-2), and 87.5 (Vero)	[13,40]
Elaeagnus angustifolia	Elaeagnaceae	NM	Leaf	Maceration/ Ethylacetate	*In vitro* model (T47D)	IC_{50}: 23.05 (T47D)	[41]
Eucalyptus camaldulensis Dehnh	Myrtaceae	NM	Leaf	Percolation/Ethanol	*In vivo* model (mice), skin cancer induced by 7,12-dimethylbenz(a) anthracene	It reduced 8-OHdG in cultured human lymphocytes in a dose-response manner, chromosomal damage, and the incidence number of tumors per animal and delayed the onset of tumors.	[42]
Gynandriris sisyrinchium L. Parl	Iridaceae	Sawsan	Leaf & bulb	Isolated compound	*In vitro* model (HL-60)	The cytotoxic activity against the human promyelocytic leukemia HL-60 cells revealed that 3′-Methyl tenuifone (refer to Fig. 2) was the most active (40 μM). The results indicate that the cytotoxicity is mediated by apoptosis.	[30,43]
Inula graveolens L.	Asteraceae	NM	Aerial parts	Decoction/Ethanol	*In vitro* model (MCF-7, T47D)	IC_{50}: 3.8 (MCF-7), 11.0 (T47D).	[25]
Inula graveolens L.	Asteraceae	NM	Aerial parts	Hydrodistillation/ Volatile oil	*In vitro* model (MCF-7, T47D)	IC_{50}: 51.5 (MCF-7), 57.2 (T47D)	[44]
Inula viscosa	Asteraceae	Taioon	Not mentioned	Isolated compounds	*In vitro* model (MCF-7, Hep-2, Vero cell)	Nepetin, IC_{50} : 5.9 (MCF-7), 11.3 (Hep-2), 103.5 (Vero cell) Hispidulin, IC_{50} : 10.4 (MCF-7), 19.5 (Hep-2), 105.5 (Vero cell)	[9,27]
Inula viscosa	Asteraceae	Taioon	Flowers	Methanol	*In vitro* model (MCF-7)	IC_{50}:15.8 (MCF-7)	[9,45]
Laurus nobilis L.	Lauraceae	Bay leaf	Fruits	Hydrodistillation/ Ethanol	*In vitro* model (T47D, MCF-7)	IC_{50} : 28 (MCF-7), 12.3 (T47D)	[46]
Laurus nobilis L.	Lauraceae	Bay leaf	Leaf	Ethanol	*In vitro* model (MCF-7)	IC_{50} : 24.49 (MCF-7)	[47]
Mandragora autumnalis Bertol	Solanaceae	Tuffah el melanin, Yabroh	Leaf	Maceration/ Ethanol, hexane	*In vitro* model (MCF-7)	MCF-7, IC_{50}: 100 (ethanol), 400 (hexane)	[48,49]
Origanum syriacum	Lamiaceae	Zaatar, Mardakoosh	Leaf	Reflux/Ethanol	*In vitro* model (MCF-7)	IC_{50} : 6.4 (MCF-7)	[9,47]
Ocimum basilicum	Lamiaceae	Habaq	Leaf	Hydrodistillation/ Volatile oil	*In vitro* model (MDA-MB-231, MCF-7, U-87 MG)	IC_{50}: 432.3 (MDA-MB-231), 320.4 (MCF-7), 431.2 (U-87 MG)	[9,50]
Ononis hirta	Fabaceae	Showk AL-Jamal	Aerial parts	Maceration/ Methanol	*In vitro* model (MCF-7)	IC_{50} : 28.0 (MCF-7)	[45]
Origanum dayi	Lamiaceae	Zaatar	Aerial parts	Reflux/Ethanol	*In vitro* model (MCF-7, T47D)	IC_{50}: 99.4 (MCF-7), 250 (T47D)	[43,51]
Pistacia atlantica	Anacardiaceae	Bottom	Leaf, galls	Hydrodistillation/ Volatile oil	*In vitro* model (MCF-7, T47D)	Leaves oil, IC_{50} : 12.9 (MCF-7), 15.7 (T47D) Gall's oil, IC_{50}:17.5 (T47D)	[52]
Pistacia palaestina Boiss.	Anacardiaceae	Bottom	Fruit	Hydrodistillation/ Volatile oil	*In vitro* model (renal cell adenocarcinoma, human amelanotic melanoma cells)	IC_{50}: 204.70 (renal cell adenocarcinoma), 356.98 (human amelanotic melanoma cells)	[36]
Salvia dominica L.	Lamiaceae	Meriamia	Leaf	Reflux/Ethanol	*In vitro* model (MCF-7, T47D, BT-474, vero)	IC_{50}: 5.8 (MCF-7), 12.9 (T47D), 14.0 (BT-474), 5.2 (Vero)	[16]
Salvia dominica L.	Lamiaceae	Meriamia	Aerial parts	Decoction/Ethanol	*In vitro* model (MCF-7, T47D)	IC_{50}: 5.8 (MCF-7), 12.83 (T47D)	[26]
Salvia fruticosa	Lamiaceae	Meriamia	Leaf	Reflux/Ethanol	*In vitro* model (MCF-7, ZR-75-1, BT-474)	IC_{50}: 25.6 (MCF-7), 18.4 (ZR-75-1), 17.4 (BT-474)	[16,53]
Salvia horminum	Lamiaceae	Meriamia	Leaf	Reflux/Ethanol	*In vitro* model (T-47D, BT-474)	IC_{50}: 25.4 (T-47D), 20.5 (BT-474)	[16,43]
Salvia triloba L.f.	Lamiaceae	Meriamia	Aerial parts	Reflux/Ethanol	*In vitro* model (MCF-7, T47D)	IC_{50} : 29.9 (MCF-7) 38.9 (T47D)	[26,49]

(*continued on next page*)

Table 2 (*continued*)

Plant species	Family	Vernacular name	Part used	Method/Solvent of extraction	Study design	Result	Reference
						The antiproliferative activities of ethanolic extracts from two *Salvia* spp were found to be due to both apoptosis and necrosis	
Salvia ceratophylla	Lamiaceae	Lessan Alhia	Leaf	Reflux/Water	*In vitro* model (HCT-116, Caco2)	IC_{50}: 28.0 (HCT-116), 9.2 (Caco2)	[43,54]
Salvia eigii	Lamiaceae	NF	Leaf	Reflux/Water	*In vitro* model (HCT-116)	IC_{50}: 30.3 (HCT-116)	[54]
Salvia greggii A.	Lamiaceae	Autumn sage	Aerial parts	Hydrodistillation/ Volatile oil	*In vitro* model (MCF-7, HCT116)	IC_{50}: 35.4 (MCF-7), 23.6 (HCT116)	[35]
Salvia syriaca	Lamiaceae	Lessan Althor	Leaf	Reflux/Ethanol	*In vitro* model (T-47D, BT-474)	IC_{50}: 24.1 (MCF-7), 23.9 (BT-474)	[16,43]
Salvia triloba	Lamiaceae	Meriamia	Leaf	Reflux/Ethanol	*In vitro* model (MCF-7)	IC_{50} 25.25 (MCF-7)	[47]
Schinus molle	Anacardiaceae	Pepper tree, pink pepper, or Brazilian pepper	Leaf	Hydrodistillation/ Volatile oil	*In vitro* model (HCT116, Caco 2, MCF-7, T47D)	IC_{50}: 43.3 (HCT116), 21.1 (Caco 2), 31.0 (MCF-7), 36.8 (T47D)	[55]
Schinus molle	Anacardiaceae	Pepper tree, pink pepper, or Brazilian pepper	Leaf	Infusion/Ethanol	*In vitro* model (HCT116, Caco 2, MCF-7, T47D)	IC_{50}: 32.8 (HCT116), 47.9 (Caco 2), 28.0 (MCF-7), 42.3 (T47D)	[55]
Silybum marianum L.	Asteraceae	Shok Aljmal, Khurfaish Aljmal	Leaf	Percolation/Ethanol	*In vivo* model (mice), skin cancer induced by 7,12-dimethylbenz(a) anthracene	It reduced 8-OHdG in cultured human lymphocytes in a dose-response manner, chromosomal damage, tumor incidence, and papilloma frequency and delayed the onset of tumors.	[9,42]
Tamarix aphylla	Tamaricaceae	Athel	Aerial parts	Maceration/ Ethanol, water	*In vitro* model (MCF-7)	IC_{50} 2.2 (water), 26.7 (ethanol), (MCF-7)	[24,43]
Viscum cruciatum Sieb.	Santalaceae	Dabaq	Leaf	Maceration/ Methanol	*In vitro* model (Burkitt's lymphoma cells)	IC_{50}: 14.21 mg/mL (Burkitt's lymphoma cells)	[33,43]
Varthemia iphionoides	Asteraceae	Ktaile	Aerial parts	Soxhlet/ Dichlorome-thane	*In vitro* (EMT6, MCF 7,T47D), *in vivo*	IC_{50}: 120 (EMT6), 270 (MCF-7), 160 (T47D)	[9,56]
Withania obtusifolia	Solanaceae	NM	Leaf	Isolated compounds	*In vitro* model (MIDA-MB-435, SW-620)	IC_{50}: 1.7 (MIDA-MB-435), 0.3(SW-620) mM	[28]

BSLT* (brine shrimp lethality test): results are expressed as LC_{50} values (mg/mL; concentration to kill 50% of the brine shrimp). EC_{50}: is a measure of the concentration of a drug, antibody or toxicant which induces a response halfway between the baseline and maximum after a specified exposure time. Green Monkey Kidney fibroblast. MDA-MB-435 human melanoma, SW-620 human colon cancer. HL-60 human promyelocytic leukemia. Caco2 Colorectal adenocarcinoma. HRT18 Rectum adenocarcinoma. A375.S2 Malignant melanoma (epithelial-like), WM1361A Malignant melanoma (melanocyte). * Lethality concentration, EC_{50} concentration to inhibit growth by 50%, LC50 concentration to kill 50% of the brine shrimp. IC_{50}: is a measurement representing the halfway point in which a compound of interest produces complete inhibition of a biological or biochemical function. NM: no mentioned.

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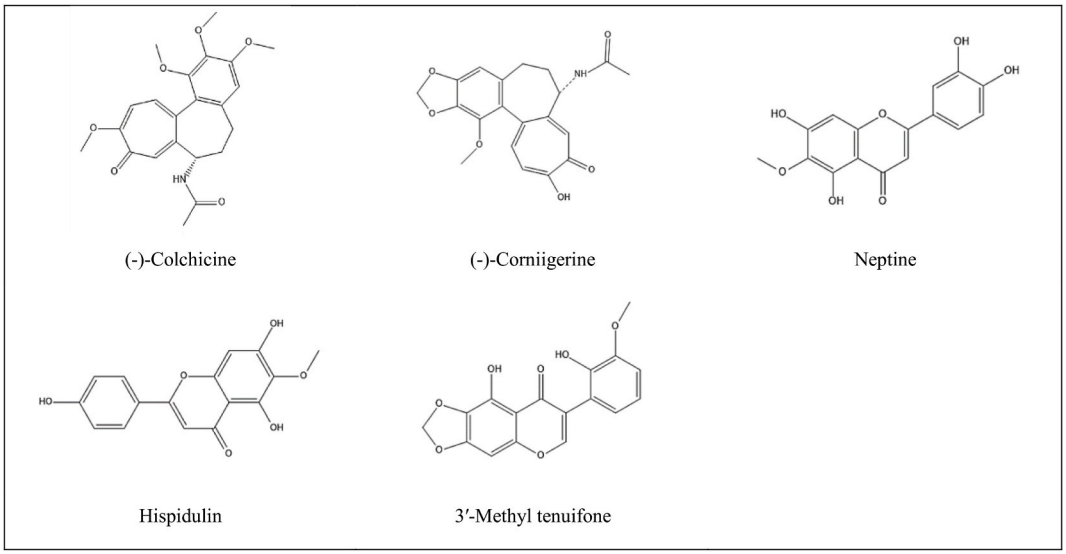

Fig. 2. Bioactive compounds isolated from different medicinal plants of Jordan with anticancer activity.

HIF-1α (Hypoxia-inducible factor 1-alpha) mRNA (messenger RNA) and VEGF protein expression under normoxic and hypoxic conditions [34,35]. An anti-migratory effect by reducing CXCL8 (C-X-C Motif Chemokine Ligand 8) levels, a chemokine that contributes to CRC (colorectal cancer) cell proliferation and metastasis [36]. Lastly, several plants have decreased DNA oxidative damage and own radical scavenging properties [37].

3.2. Medicinal plants with antimicrobial activity

Resistance to antimicrobial medications is a global threat [49]. However, plants always fuel us with various bioactive compounds that can be used to develop new medicines as antibiotics [49]. The antimicrobial activity of Jordanian plant extracts and volatile oils have been investigated. Many researches exhibited promising antimicrobial activities of these plants in pharmaceutical and food preservation systems. A total of 131 plant species were investigated for their antimicrobial activities as shown in Tables 3 and 4. These plant species were found to belong to 49 plant families. After scrutinizing the literature, it was determined that Asteraceae (n = 40), Lamiaceae (n = 32), and Fabaceae (n = 12) were the prominent three families according to the number of species studies conducted in this domain of research. *Varthemia iphionoides* (n = 6), *Teucrium polium* (n = 5), *Achillea fragrantissima* (n = 4), *Gundelia tournefortii* (n = 4), *Inula viscosa* (n = 4), for example, were the five most studied species which are also common herbs in the traditional medical system. Therefore, they can be utilized as food or are easily accessible targets for scientific research.

3.2.1. Plant tissue, extract and bacteria types

This review revealed that 47% of the plant extracts explored in the 60 papers were extracted from leaves, and more than 30% were from aerial parts. The subsequent most common part was the flowers (26%). The crude ethanolic extracts were the most common (37%), followed by the methanolic extracts (32%), aqueous extracts (16%), ethylacetate extracts (6%), hexane extracts (4%), and chloroform extracts (3%). It was also found that *Staphylococcus aureus* was the most targeted Gram-positive bacteria (69%) including methicillin-resistant *staphylococcus aureus* (MRSA), followed by *Bacillus subtilis* (17%), *Bacillus cereus* (1%), *Streptococcus pneumonia* (2%), *Enterococcus faecalis* (1.5%), *Staphylococcus epidermidis* (1%), *Micoroccocus luteus* (2%) and *Propionibacterium acne* (6%). On the other hand, *Escherichia coli* was the most targeted Gram-negative bacteria (35%), followed by *Pseudomonas aeruginosa* (27%). The other strains were *Enterobacter aerogenes* (1.7%), *Enterobacter cloacae* (3.4%), *Proteus mirabilis* (1.7%), *Klebsiella pneumonia* (14%) *Salmonella paratyphi* (1.6%), *Proteus vulgaris* (2.1%), *Proteus mirabilis* (2%), *Erwinia carotovora* (1.2%), *Helicobacter pylori* (6.7%), and *Chromobacterium violaceum* (3.3%). Figs. 3–5 provide further details on the topic as follows.

The majority of studies conducted illustrated that the Araceae family had the highest overall mean diameter zone of inhibition (DZI) against Gram-negative and positive bacteria. The DZI for Gram – negative and positive respectively were (22.30 mm, 22.63 mm) [57–61]. The other families that were studied against Gram-negative for their antimicrobial activities were (Apiaceae, Asteraceae, Fabaceae, Rosaceae, Lamiaceae) with DZI values ranging from 15.7 to 38 mm [62–72]. Among solvents used for extraction, acetone showed the best (highest) mean DZI (17.4 mm), while hexane extracts were the lowest (7.4 mm). On the other hand, ethyl acetate extracts were the most potent (MIC 0.3 mg/mL), while methanol extract was the least potent (MIC 8.8 mg/mL). Seeds extract had the

Table 3
Asteraceae antimicrobial activity against Gram-positive bacteria.

Scientific name	Method of extraction/Part used	The concentration of plant extract	Type of bacteria	Antimicrobial effect (DZI, MIC)	Reference
Achillea fragrantissima	Soxhlet, Aerial parts	400 μg/mL	*S. aureus*	MIC (mg/mL): 2.9 (80% methanol)	[63]
	Maceration, whole plant	0.97–250 mg/mL	*S. aureus,* MRSA	DZI (mm): 7,7 (methanol)	[67]
	Maceration, whole plant	200 mg/mL	*S. aureus*	DZI (mm): 19.5 (95% ethanol)	[84]
	Decoction, aerial parts	5–100 mg/mL	*S. aureus*	MIC (mg/mL): 25 (water), 6.25 (alcohol)	[81]
			MRSA	MIC (mg/mL): 12.5 (alcohol)	
			S. pneumoniae	DZI (mm): 12.5 (water), 3.12 (alcohol)	
			B. cereus	MIC (mg/mL): 1.56 (alcohol)	
			E. faecalis	MIC (mg/mL): 12.5 (alcohol)	
	Maceration, aerial parts	2 mg/disc	*S. aureus, B. subtilis, M. luteus*	DZI (mm): 24, 8.5, 9.16 (80% methanol)	[87]
Achillea biebersteinni	Maceration, aerial parts	5–100 mg/mL	*S. aureus*	DZI (mm): 17.2 (95% ethanol)	[84]
	Reflux, whole plant	5–100 mg/mL	*S. aureus*	MIC(mg/mL): 6.25 (hydro-alcoholic), 25 (water)	[83]
			MRSA	MIC (mg/mL): 3.12 (hydro-alcoholic), 25 (water)	
			S. pneumoniae	MIC (mg/mL): 1.56 (hydro-alcoholic)	
			B. cereus	MIC (mg/mL): 1.56 (hydro-alcoholic)	
			E. faecalis	MIC (mg/mL): 12.5 (hydro-alcoholic	
	Maceration, flowers	100 μg/mL	*P. acne*	MIC(mg/mL): 10 (methanol)	[91]
Achillea falcata	Reflux, aerial parts	5–100 mg/mL	*S. aureus*	MIC (mg/mL): 50 (water)	[82]
	Reflux, aerial parts	5–100 mg/mL	*S. aureus*	MIC (mg/mL): 6.25 (ethanol 70%)	
	Reflux, aerial parts	5–100 mg/mL	MRSA	MIC (mg/mL): 12.5 mg/mL (ethanol 70%)	
	Reflux, aerial parts	5–100 mg/mL	*E. faecalis*	MIC (mg/mL): 12.5 mg/mL (ethanol 70%)	
Achillea millefolium	Maceration, plantlet	Ethanol 40 mg/100 μl and water 30 mg/100 μl	*S. aureus*	DZI (mm): 19.0 (water), 20.8 (ethanol)	[94]
Achillea membranacea	Maceration, leaves	500 mg/mL	*S. aureus*	DZI (mm): 19 (ethanol), 12.3 (methanol)	[57]
	Maceration, leaves	500 mg/mL	*S. aureus*	DZI (mm): 16.0 (water), 13.7 (ethanol), 30.3 (methanol), 12.7 (acetone)	
			MRSA	DZI (mm): 26.3 (water), 20.7 (water), 14.3 (methanol), 19.7 (acetone)	
Achillea santolina	Maceration, NM[a]	200 mg/mL	*S. aureus*	DZI (mm): 11.2	[84]
Achillea tomentosa	Steam distillation, aerial parts	100 μL of the diluted Volatile oil per each agar well.	*S. aureus, B. subtilis*	(RIZD 103 ± 4.73%), (RIZD 80%)	[95]

[a] NM: not mentioned. *S. aureus* (*Staphylococcus aureus*), *B. subtilis* (*Bacillus subtilis*), *M. luteus* (*Micoroccocus luteus*), *S. pneumoniae* (*Streptococcus pneumoniae*), *K. pneumoniae* (*Klebsiella pneumoniae*), *B. cereus* (*Bacillus cereus*), *E. faecalis* (*Enterococcus faecalis*), *P. acne* (*Propionibacterium acne*).

Table 4
Asteraceae antimicrobial activity against Gram-negative bacteria.

Scientific name	Part used	The concentration of plant extract	Type of bacteria	Antimicrobial effect (DZI, MIC)	Reference
Achillea fragrantissima	Maceration, whole plant	200 mg/mL	*K. pneumonia*	DZI: 10.2 mm (ethanol)	[84]
Achillea fragrantissima	Maceration, aerial parts	2 mg/disc	*K. pneumonia, E. coli*	DZI: 9, 9 mm (methanol)	[87]
Achillea fragrantissima	Soxhlet, aerial parts	400 μg/mL	*E. coli, P. aeruginosa, E. cloacae, P. mirabilis*	DZI: 23, 18, 18, 17 mm (methanol)	[63]
Achillea fragrantissima	Decoction, aerial parts	5–100 mg/mL	*K. pneumoniae*	MIC (mg/ml): 12.5 (hydro-alcohol)	[81]
Achillea biebersteinni	Maceration, whole plant	200 mg/mL	*K. pneumonia, E. coli, E. cloacae*	DZI: 8.5 mm, 8.5 mm, 9 mm (ethanol)	[84]
Achillea biebersteinii	Whole plant	5–100 mg/mL	*K. pneumoniae*	MIC: 25 mg/mL (water), 3.12 mg/mL (hydro-alcoholic).	[83]
Achillea membranacea	Maceration, leaves	500 mg/mL	*S. typhimurium, P. aeruginosa, E. coli*	20 mm (ethanol), 25 mm (ethanol), 17.3 mm (ethanol), 16.3 mm (methanol).	[57]
Achillea millefolium	Maceration, plantlet	30 mg/100 μl	*S. paratyphi, P. vulgaris, K. oxytoca, Proteus mirabilis*	DZI: 21.2, 19.6, 14.4, 14.5 mm (water)	[94]
Achillea millefolium	Maceration, plantlet	40 mg/100 μl	*S. paratyphi, P. vulgaris, K. oxytoca, P. mirabilis*	DZI: 20.2, 19.8, 10.33, 10.33 mm (ethanol)	
Achillea falcata	Reflux, aerial parts	5–100 mg/mL	*K. pneumoniae*	MIC: 12.5 mg/mL (70% ethanol)	[82]
Achillea santolina	Maceration, whole plant	200 mg/mL	*K. pneumonia, E. cloacae*	DZI: 9 mm, 12 mm (ethanol)	[84]
Achillea tomentosa	Steam distillation, aerial parts	100 μL of the diluted volatile oil	*P. aeruginosa*	RIZD 90% (Volatile oil)	[95]

K. pneumoniae (*Klebsiella pneumoniae*), *B. cereus* (*Bacillus cereus*), *E. faecalis* (*Enterococcus faecalis*), *P. acne* (*Propionibacterium acne*), *E. coli* (*Escherichia coli*), *P. aeruginosa* (*Pseudomonas aeruginosa*), *P. mirabilis* (*Proteus mirabilis*), *E. cloacae* (*Enterobacter cloacae*), *S. typhimurium* (*Salmonella typhimurium*), *S. paratyphi* (*Salmonella paratyphi*), *P. vulgaris* (*Proteus vulgaris*) *K. oxytoca* (*Klebsiella oxytoca*).

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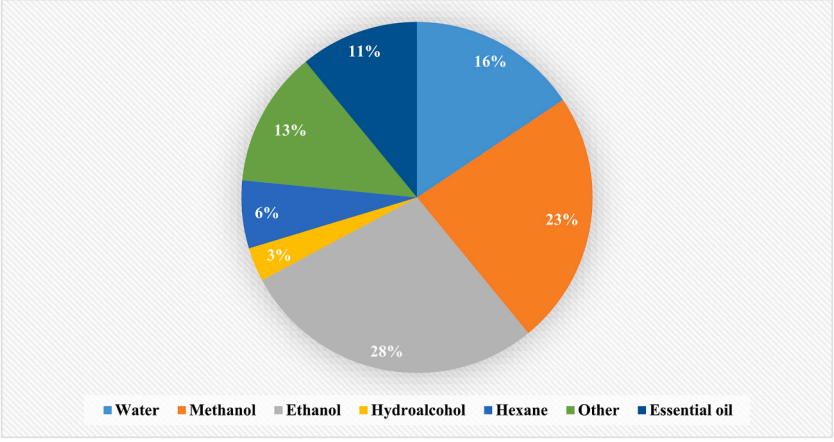
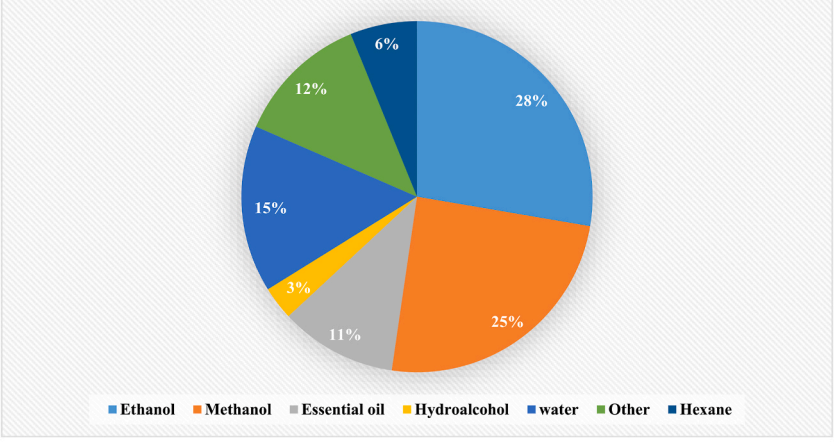


(A)



(B)

Fig. 3. (A) Plant tissues extracted to test against Gram-negative bacteria, (B) Method of extraction used to create the extract.

highest mean diameter zone of inhibition (18.4 mm), while flowers had a low MIC value (0.86 mg/mL). *Helicobacter pylori* is the most affected bacteria species in comparison to other bacteria species.

On the other hand, several solvents were used to investigate the antimicrobial activity against Gram-positive bacteria, among which acetone showed the best (highest) mean DZI (17.57 mm), while chloroform extracts were the lowest (6.5 mm). On the other hand, ethyl acetate showed the best (lowest) mean MIC (0.41 mg/mL), while water showed the highest MIC (14.2 mg/mL). Flowers extract has the highest mean DZI (18.26 mm). While leaves have the lowest MIC values (1.3 mg/mL).

3.2.2. Plant families antimicrobial activity

3.2.2.1. Araceae. Over 800 species of Araceae are of economic importance in ornamental, edible and medicinal uses [73]. This family is represented in Jordan by three genera and five species, namely *Arum palestinum*, *Arum dioscoridis*, *Arum hygrophilum*, *Biarum angustatum* and *Eminium spiculatum* (Blume) Kuntze [74]. Many species are used in traditional medicine, such as *Arum discoridis* and *Arum hygrophillum*, collectively called Louf, which is used for treating circulatory system problems and internal bacterial infection and as a spice and cooked [57,58].

Several studies evaluated the antibacterial activity of *Arum discoridis* and *Arum hygrophillum* leaves aqueous extract and revealed broad spectrum of inhibition. Additionally, the ethanol and water extracts had broad-spectrum antimicrobial activity against MRSA, *Staphylococcus aureus*, *Bacillus subtilis*, *Staphylococcus epidermidis*, *Salmonella typhimurium*, *Listeria monocytogenes*, *Pseudomonas*

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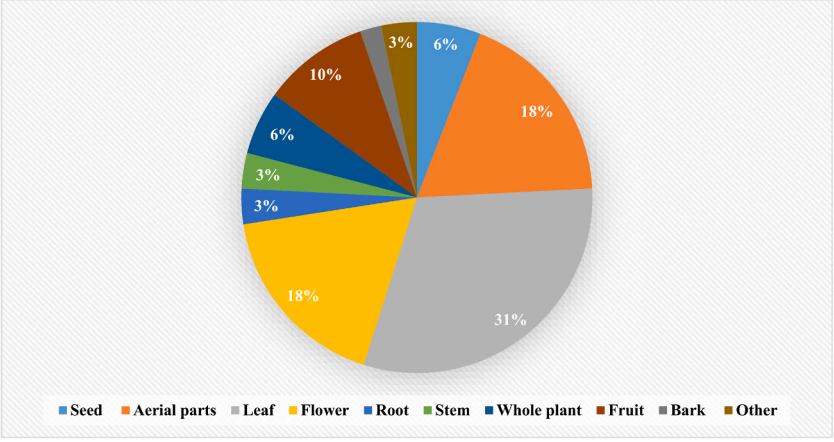
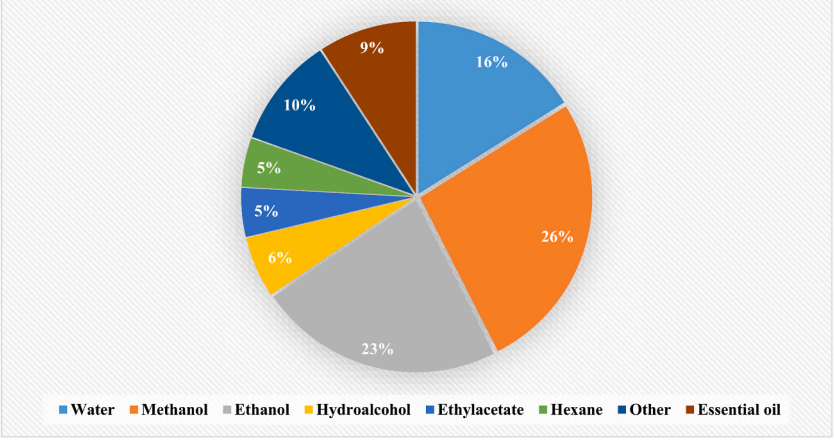


(A)



(B)

Fig. 4. (A) Plant tissues extracted to test against Gram-positive bacteria, (B) Method of extraction used to create the extract.

aeruginosa and *Escherichia coli*, with a DZI ranges from 20 mm to 36 mm [57–59]. Literature also revealed that *Eminium spiculatum* aqueous stem extract -the only representative of the genus *Eminium* grown wild in Jordan-had potential antibacterial activity against MRSA (DZI: 21.7 mm) and *Pseudomonas aeruginosa*. Moreover, the aqueous leaf extract shows inhibitory activity against *Escherichia coli* [74]. *Arum palestinum* showed activity towards *Propionibacterium acne* with MIC of 0.125 mg/mL [61].

3.2.2.2. Apiaceae. The Apiaceae (Umbelliferae) family comprises many genera used as culinary herbs and in folk medicine [75]. In addition, many plant species were used to improve the antimicrobial activity of conventional antibiotics, including *Pimpinella anisum* and *Lepidium sativum* [76].

Ammi visnaga (known as Khella) extract showed a significant inhibitory effect on *Escherichia coli* at (MIC: 800 ppm), possessing activity against *Pseudomonas aeruginosa* (MIC 3000 ppm), *Staphylococcus aureus* (MIC: 4000 ppm) and *Candidca albicans* (MIC: 2000 ppm) [77]. Using the volatile oils extracted from *Foeniculum vulgare*, *Anethum graveolens*, *Coriandrum sativum*, and *Apium graveolens* against *Bacillus subtilis.* It was also established that *Apium gravelones* (MIC: 1.25 mg/mL) had the best antibacterial activity amongst the family [75].

Studies highlighted that *Pimpinella anisum* and *Ducrosia flabellifolia* exhibited moderate antimicrobial activity against *Staphylococcus aureus* and weak activity against *Escherichia coli* [64,78]. The volatile oils of *Foeniculum vulgare* leaves showed growth inhibitory activity against *Bacillus subtilis* with MICs 10 mg/mL. In addition, the fennel seed oil had similar activity against Gram positive and Gram negative bacteria [75].

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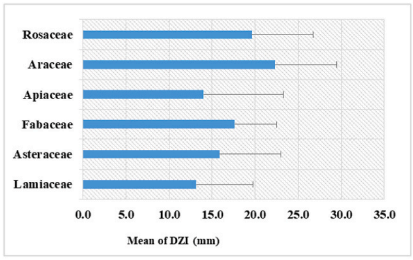
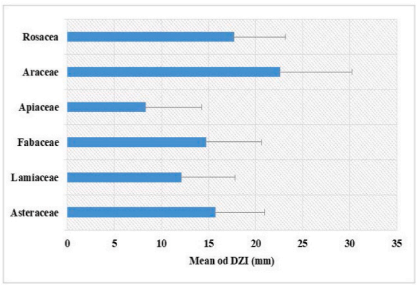


Fabaceae	*		
Asteraceae	*		
Rosaceae	*		
Araceae	*	*	*
	Lamiaceae	Asteraceae	Apiaceae

A



Lamiaceae	*	*			
Fabaceae					
Apiaceae	*	*	*		
Araceae	*		*	*	*
	Asteraceae	Rosacea	Fabaceae	Lamiaceae	Apiaceae

B

Fig. 5. Mean and standard deviation of diameter zone of inhibition (DZI) of extracts in the top six families, with significant differences in DZI values (mm) for (A) Gram-negative bacteria and (B) Gram-positive bacteria reported. *: $p < 0.05$.

3.2.2.3. Asteraceae. The Asteraceae (Compositae) family comprises over 1600 genera and 2500 species and is the most prominent flowering plant family. For centuries, it has been used in diet and medicine [79]. Members of this family share similar chemical composition and demonstrate several pharmacological effects such as antioxidant, anti-inflammatory, diuretic, wound healing and antimicrobial activities [79], (Tables 3 and 4).

The genus *Achillea* (commonly referred to as yarrow) is mainly distributed in the northern hemisphere, most indigenous to Europe and the Middle East. *Achillea* species are widely used in popular medicine of several cultures due to numerous pharmacological properties, such as analgesic, healing, anti-inflammatory, antioxidant, antispasmodic, antihemorrhoidal, stomachic, antiseptic and emmenagogue [80,81]. The genus *Achillea* has been studied in several researches [63,67,76,82,83]. Traditionally, it has been used to treat severe illnesses since ancient times and known as Qaisoum [84]. The best results were revealed by *Achillea biebersteinii* extracts which illustrated activity against several bacterial types except for *Pseudomonas aeruginosa*. The most susceptible of the Gram-positive bacteria was *Streptococcus pneumoniae*, *B. cereus* and *Staphylococcus aureus*, and of the Gram-negative was *Klebsiella pneumoniae*. The results differ by the type of extract and the part of the plant used [83–85].

Inula viscosa is widely distributed and used to treat several medical conditions, including wounds, intestinal worms, respiratory tract disorders, bone, blood pressure, and diabetes [27]. The crude extracts of *Inula viscosa* were active against bacterial strains *Staphylococcus aureus*, *Bacillus subtilis*, *Propionibacterium acne*, MRSA and *Pseudomonas aeruginosa,* inactive against *Escherichia coli*, *Candidca albicans* and *Aspergillus niger* [61,86–88]. *Inula viscosa* is used widely in treating gastroduodenal disorders. In one study, the ethanolic crude extract showed intense activity against different isolates of *Helicobacter pylori* with an MIC of 83 mg/mL and MBC of 104 mg/mL [89].

Centaurea damascena is another plant studied for its antimicrobial activity. Traditionally, it is used to treat gastritis and as a condiment for hot tea. Several Gram-positive and Gram-negative bacteria were susceptible to *Centaurea damascena* methanol extract. The MIC ranges from 0.123 mg/ml to 1.1 mg/mL. For example, the MIC against *Staphylococcus aureus*, *Bacillus subtilis* and *Enterobacter aerogenes* was 0.123 mg/mL [90].

Other plants as *Cichorium pumilum* and *Chrysanthemum coronarium* had moderate antimicrobial activity against *Propionibacterium acnes* (MIC 2.5 mg/mL), *Staphylococcus aureus* (DZI: 20 mm), *Bacillus subtilis* (DZI: 19 mm) and *S. epidermidis* (DZI: 18 mm) [85,91]. Also, *Sonchus oleraceus* exhibited prominent antiquorum sensing activity (18 mm) [92]. Alqudah et al. studied *Geropogon hybridus's* antibacterial activity against both Gram-positive and Gram-negative bacteria and showed the highest potency (IC_{50} 0.83 mg/mL) against *Escherichia coli* [62]. *Gundelia tournefortii* leaves extract also showed antibacterial activity against Gram-positive as *Staphylococcus aureus, Salmonella typhimurium and* MRSA (DZI: 15.7–16.7 mm). And Gram-negative pathogens as *Pseudomonas aeruginosa* and *Escherichia coli* (DZI: 14.3–10.7 mm) [60].

Moreover, two species of *Onopordum* were investigated, namely, *Onopordum blancheanum* and *Onopordum jordanicolum*. Generally, *Onopordum jordanicolum* exhibited antibacterial activity against *Staphylococcus aureus*, MRSA, *K. pneumonia*, and *P. mirabillis*. The

ethanol extract of flowers displayed significant antibacterial activity against *Staphylococcus aureus* with the best MIC and MMC (minimum microbial concentration) values. In addition, the acetone extract displayed significant antifungal activities against *Aspergillus brasiliensis* and *Candidca albicans* with the best MIC and MMC values. On the other hand, the flower extracts of *Onopordum blancheanum* produced antibacterial and antifungal activities against *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia*, and *Proteus mirabillis*, *Aspergillus brasiliensis* and *Candida albicans* [93].

Different Artemisia species as *Artemisia herba–alba*, *Artemisia sieberi*, and *Artemisia inculata* were investigated against several bacteria species. *A. herba-alba* extract was found to possess a high inhibitory effect on *Staphylococcus aureus* at MIC 3000 ppm, (DZI: 14–16 mm), *Pseudomonas aeruginosa* at MIC 4000 ppm, and *Escherichia coli* at MIC 4000 ppm (DZI 17 mm) [77]. Conversely, *Artemisia sieberi* exhibited weak inhibitory activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Enterobacter cloacae* [70]. Moderate antimicrobial activity against *Helicobacter pylori* was observed when *Artemisia inculata* ethanol extract was tested [89].

3.2.2.4. Fabaceae. The Fabaceae (Leguminosae) is one of the most prominent flowering plant families. These plants have been the main part of meals in arid and semiarid regions since 6000 BCE due to their protein richness [74]. There is also proof of humans' use of these plants in Asia, Europe, and North America for medicinal purposes. Recently, species of this family have been found naturally or are cultivated everywhere around the globe except the poles [96,97]. Phytochemical metabolites of Fabaceae have industrial and medicinal importance. This family is a rich source of phytochemicals, including alkaloids, flavonoids, lectins, saponins, carotenoids, and phenolic acids, which have anticancer properties, and the use of such phytochemicals is increasing over time [97].

It was found that *Alhgi graecorum,* for example, exhibited antimicrobial activity in a dose-dependent manner against several bacterial isolates. The MIC was between 1.1 and 1.8 mg/mL [63].

Lupinus varius was also found to display a broad spectrum of antimicrobial activity. The seed extract exhibited high antibacterial activity against *Pseudomonas aeruginosa* with a mean inhibition zone of 28.7 ± 1.5 mm and antifungal activity against *Candida albicans* with a mean inhibition zone of 31.3 ± 0.6 mm. Surprisingly, it was highlighted that MRSA and *Escherichia coli* were susceptible to all parts of *Lucius varius*, both aqueous and alcohol extracts of leaf and alcohol extracts of the flower. They showed inhibition zone values ranging from 15.0 ± 1.0 to 24.0 ± 2.0 mm for MRSA and from 9.3 ± 1.5 mm to 19.0 ± 1.0 mm for *Escherichia coli* [57,60].

Furthermore, Lathyrus hirticarpus leaves extract exhibited broad antibacterial activity spectrum. It showed an inhibition zone of 17.3 mm for S. pyogenes using the methanol extract, 21.7 mm and 19.3 for *Staphylococcus aureus* and *Klebsiella pneumonia*, respectively using acetone extract, 20.67, 30.3 for *Pseudomonas aeruginosa* and *Proteus mirabilis* respectively using the aqueous extract, 22.33 mm for *Escherichia coli* using the methanol extract [93].]. In addition, the ethanol extract exhibited antifungal activity against *Aspergillus brasiliensis* and *Candida albicans* [93]. Moderate activity was observed using *Ononis natrix* against Gram-positive *Bacillus subtilis* and *Brevibacillus brevis*, and the Gram-negative *Escherichia coli* [72]. It is also noteworthy that the n-hexane extracts of the aerial parts of *Ononis hirta* showed enjoyable activity against *Pseudomonas aeruginosa* at MIC of 0.125 g/mL [88].

3.2.2.5. Lamiaceae. Lamiaceae, or the mint family, is known for its economic value. It is reputation comes from the aromatic scene within its leaves and flowers. *Salvia* is the most well-known genus of the Lamiaceae family. Its antimicrobial activity has been established in the literature [98]. Different studies demonstrated a weak to moderate antimicrobial activity against Gram-positive bacteria as *Staphylococcus aureus*, MRSA, *Bacillus subtilis*, and *Brevibacillus brevis*, with inhibition zone values ranging from 9 to 16.2 mm. It also demonstrated weak activity against *Escherichia coli* and *Klebsiella penumonia* with an inhibition zone of 5–10 mm, refer to Tables 3 and 4.

Teucrium polium extracts exhibited a different degree of antimicrobial activity. The most interesting activity was for n-hexane extract of the aerial parts against *Pseudomonas aeruginosa* with an MIC value of 125 μg/mL [88]. Moreover, the MIC of *Rosmarinus officinalis* ranges between 1.0 and 1.2 mg/ml against *Staphylococcus aureus*, MRSA (MIC: 0.5 1.5 mg/ml), and *Propionibacterium acne* (0.5 mg/ml) [67,70,92]. The Gram-negative bacteria are more susceptible to *Rosmarinus officinalis* extracts, especially *Escherichia coli* (0.9 mg/ml) [63].

Thymus is another well-known species. The leaves of *Thymus capitatus* possess stronger antimicrobial activities than stem extracts against the bacterium *Staphylococcus aureus* and the bacterium *Pseudomonas aeruginosa* [65]. In another study, *Thymus capitatus* leaves extract exhibited broad-spectrum activity as it successfully inhibited the growth of several tested microorganisms with varying degrees. The results of the disc diffusion method indicated that *Pseudomonas aeruginosa* was the most sensitive strain (22 mm), followed by *Staphylococcus aureus*, *Enterobacter aerogenes* and *Escherichia coli* [65,99]. It was also found that the volatile oils of *Thymus serpyllum* and *Thymus vulgaris* produced inhibition zones of 8–20 mm and 5–20 mm, respectively [64].

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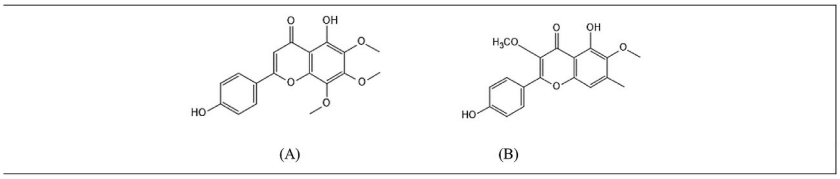

Fig. 6. Isolated flavonoids with antiplatelet activity. (A) Xanthomicrol, (B) Kumatokenin.

Origanum jordanicum methanol extract had growth inhibitory activity against *Staphylococcus epidermidis* at 0.781 mg/mL MIC [100]. On the other hand, the volatile oils of *O. syriacum* had significant antimicrobial activity against *Propionibacterium acne* (MIC 1 mg/ml) and moderate activity against *H. pylori* [89,91]. Additionally, *Mentha rotundifolia* and *Origanum syriacum* were tested against *Propionibacterium acne;* the MIC was 2 and 1 mg/mL, respectively [91].

Lavandula angustifolia had moderate inhibitory activity against Gram-positive bacteria with a DZI range from 9.5 to 15 mm and weak antibacterial activity against Gram-negative bacteria 7–10.5 mm [92]. *Lavandula officinalis* showed good activity against *Helicobacter pylori* isolate I and II with diameter zone of inhibition 32 (mm) and 35 mm, respectively [89]. *Origanum jordanicum* was used by the Bedouin of Petra for ages for food and medicine. The methanol extract demonstrated paramount results against *Staphylococcus epidermidis* at 0.781 mg/mL MIC, and it was effective against *Candida albicans* [69]

3.2.2.6. Rosaceae. The extracts of *Sarcopoterium spinosum* were found to be effective against several tested bacterial strains. At relatively low concentrations, it exhibited that it can completely inhibit the growth of Gram-positive bacteria (*Staphylococcus aureus* 0.5 mg/ml, *Bacillus subtilis* 1 g/ml, *Micrococcus luteus* 1 mg/ml). Nonetheless, Gram-negative bacteria were inhibited at higher concentrations (*Escherichia coli* 1 mg/ml, *Klebsiella penumonia* 2 mg/ml) [87]. One study illustrated that the methanolic and ethanolic leaf and fruit extracts of *Rubus sanguineus* have significant inhibitory activity against Gram-positive bacteria (DZI: 18–22 mm) and Candida. Yet, they have not shown any significant activity against Gram-negative bacteria [101].

3.3. Medicinal plants with antiplatelet activity

The leaves and flowering tops of *Varthemia iphionoides* were used to assess the antiplatelet activity. *In vitro* antiplatelet activity was investigated for the aqueous and alcoholic extracts of the plant, for the isolated volatile oil, and four different isolated flavonoids, including xanthomicrol, kumatokenin, jaceidin and 3, 3V-di-O-methyl quercetin (refer to Fig. 6). The aqueous extract, xanthomicrol, and kumatokenin showed antiplatelet activity, while the volatile oil and the alcoholic extracts did not. The antiplatelet activity of the aqueous extract has been shown to follow a concentration-dependent manner against both collagen and adenosine diphosphate (ADP); concentrations of 30 and 20 Ag/ml exhibited complete inhibition [102].

Rheum palaestinum, traditionally used in Jordan, was evaluated for its antiplatelet activity by using the aerial parts of the plant. The antiplatelet activity was investigated for two stilbene derivatives that were isolated and identified. These structures were detected via spectroscopic data, including MS and NMR. The two stilbenes were *trans*-resveratrol-3-O-b-d-glucopyranosid (Piceid) and rhapontigenin-3-O-b-d-glucopyranoside (rhaponticin), refer to Fig. 7. Upon examination, the two stilbenes showed antiplatelet activity on human platelet-rich plasma (PRP) aggregation induced by collagen and ADP [103].

The antiplatelet activity of *Gundelia tournefortii* was also evaluated using the aerial parts of the plant, and five compounds were isolated, including scopoletin, isoscopoletin, esculin, and a mixture of b-sitosterol and stigmasterol. A Hydrodistillation technique was used to obtain the volatile oil. The antiplatelet activity of the plant was tested *in vitro,* relying on adenosine-50-diphosphate (ADP) and arachidonic acid (AA) as agonists. Only the chloroform extract has expressed mild inhibitory activity on platelet aggregation induced by ADP and arachidonic acid (AA) [104].

Full antiplatelet aggregation activity was observed by methanolic extracts of aerial and root parts of *Aristolochia maurorum*, the acidic fractions, aristolochic acid standard, the aristolochic acid I, II, and their combination. This antiplatelet activity was observed to be variable between the two phases of platelet aggregation based on concentration [105]. Furthermore, the platelet aggregation Inhibitors derived from aerial Parts Grown in Jordan were also assessed, and multiple compounds were isolated from the plant, including a flavonoid glycoside (rutin) and several minor compounds.

The antiplatelet activity for the crude methanolic and ethylacetate extracts of *Ruta chalepensis* and three major isolated compounds was measured by the aggrometric method for measuring aggregation. Both ethylacetate and methanol extracts exhibited inhibitory activity against ADP- induced platelet aggregation (ADP-IA). However, only ethylacetate extract showed activity on collagen-induced platelet aggregation (Co-IA). In addition, Bergapten exhibited more inhibitory activity against ADP-IA than chalepensin, which expressed more activity against Co-IA than bergapten [106].

The volatile oil obtained from air-dried aerial flowering parts of *Achillea bieberstienii* showed dose-dependent solid inhibition of platelet aggregation caused by ADP (10 μM) and collagen (2 μg/mL). Furthermore, it was noticed that at lower concentrations (10 and 20 μg/mL), the essential oil showed higher antiplatelet activity against ADP-induced aggregation compared to collagen-induced

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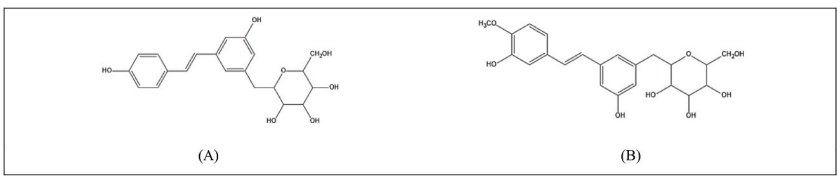

Fig. 7. Isolated stilbenes with antiplatelet activity. (A) Resveratrol 3-O-d-glucopyranoside, (B) Rhapontigenin 3-O-d-glucopyronoside.

aggregation. And, at higher concentrations (50 and 60 μg/mL), complete inhibition of aggregation induced by ADP and collagen was achieved [107]. In addition, both α-terpinene and p-cymene showed a concentration-dependent increase in the inhibitory activity [107]. This review also found that several concentrations of *Achillea biebersteinii* extracts showed a non-dose-dependent enhancement of platelet aggregation induced by adenosine diphosphate (ADP) and collagen [83].

3.4. Medicinal plants with antidiabetic activity

Using crude plant extracts to treat diabetes is seen as a practice in traditional medicine in Jordan. It was documented around 70 species indigenous to Jordan are used traditionally to treat diabetes [108]. Therefore, several plants were evaluated for their *in vivo/in vitro* hypoglycemic activities [108]. Some of these plants exhibited dual or mono alpha-amylase and glucosidase activity, like *Aloe vera*, *Arum dioscoridis*, *Arum palaestinum*, *Arum hygrophilum*, *Crataegus aronia*, *Adiantum capillus-veneris*, *Origanum syriacum*, *Geranium graveolens*, *Varthemia iphionoides*, *Paronychia argentea*, *Rosmarinus officinalis* and *Olea europaea* [109–116].

Both *Achilla santolina* and *Eryngium creticum* exhibited a dose-dependent pancreatic β-cell proliferation [117].]. In addition, *Geranium graveolens and Varthemia iphionoides* augmented β-cell mass expansion [118]. On the other hand, *Pistacia atlantica* augmented acute β cell insulin secretory activity and the integrity of cells [117]. Also, *Sarcopoterium spinosum* showed insulinotropic and proliferative effects in the pancreas [118].

The blood glucose data obtained indicate that aqueous extract from *Alkanna strigosa* produced hypoglycemic effects in alloxan-induced diabetic rats similar to a standard antidiabetic drug, metformin, by enhancing insulin production and decreasing glucagon production [119].

Collectively, using different assay techniques for *in vivo* and *in vitro* models the antidiabetic activity for Jordanian plants and herbs was confirmed by majority of research, presented their proposed mechanism of actions. Similar to conventional antidiabetic drugs, the Jordanian herbs exhibited secretagogue activity, inhibition of hepatic gluconeogenesis and intestinal carbohydrate absorption, and enhancement of glucose uptake by adipose and muscle tissues [120].

3.5. Medicinal plants with anti-hyperlipidaemia activity

The pharmacological inhibition of dietary lipid digestion and absorption can induce favorable amelioration of dyslipidemia, atherosclerosis and obesity. *Adiantum capillus-veneris,* for instance, exerted marked triacylglycerol-reducing capacities at levels higher than atorvastatin [109].

In a dose-dependent manner, *Arum* species, *Anthemis palaestina*, *Lavandula angustifolia*, *Origaum syriacum*, *Salvia triloba* and *spinosa*, *Ononis natrix*, *Fagonia arabica*, *Majorana syriaca*, *Malva nicaeensis*, *Rosmarinus officinalis*, *Hypericum triquetrifolium*, *Chrysanthemum coronarium*, *Paronychia argentea* were reported to inhibit the gastric absorption of triglycerides by the inhibition of pancreatic lipase [111,114,121–124]. Additionally, one study highlighted that the administration of the aerial parts extract of *Alkanna strigosa* resulted in a significant reduction in the mean values of serum cholesterol, triglyceride, and LDL and an increase in the mean values of HDL [119].

3.6. Medicinal plants to treat gastrointestinal tract disorder

Many herbal extracts are used in folk medicine to treat digestive disorders, including peptic ulcers. *Helicobacter pylori* is one of the most prevalent human infections and have been implicated as a predisposing factor for peptic, duodenal ulcer, chronic active gastritis, gastric cancer and lymphoma [89,125]. The Peels extract of *Punica granatum* displayed a significant inhibitory effect on *Helicobacter pylori* growth and urease enzyme activity. In addition, it showed a synergistic and a reduction in the MIC of metronidazole four-fold [126].

3.7. Medicinal plants of Jordan: miscellaneous

3.7.1. Female antifertility and abortifacient effects

Inula iscosa leaf extract exhibited the anti-implantation and mid-term abortifacient effects in rats. The aqueous extract administered in the first days of gestation caused diminished fetal implantation and reduced the number of corpora lutea and blood progesterone levels. Moreover, its administration on mid-term gestation caused abortion [127]. It was also underlined that *Artemisia monosperma* leaves are taken in folk medicine by certain women of Jordan for abortion induction. The plant outcome in pregnant rats was assessed using the ethanolic leaves extract. The intraperitoneal administration of 150 mg/kg or 300 mg/kg of the plant ethanolic extract at different gestation times causes severe harm to rat pregnancy outcomes [128,129].

3.7.2. Anti-gout effect

The methanol extract of *Salvia spinose* had a potent inhibition of xanthine oxide *in vitro*. However, a further biological investigation is needed to verify the reported inhibitory activity using an animal model [130].

3.7.3. Anti-inflammatory

The methanolic extracts of *Urtica pilulifera* leaves had a significant anti-arthritic effect. It also exhibited an inhibitory effect by inhibiting paw swelling, skin lesions, and articular deformity [131]. The proanthocyanidins fraction of *Cistus incanus* inhibited

TPA-induced edema, and the pure isolated compounds inhibited COX 1 and COX 2 with high selectivity toward COX 2 In addition, *Eucalyptus globulus* and *Arum palaestinum* revealed a remarkable inhibitory activity against IL-1a proinflammatory cytokines [61].

3.7.4. Anticholinesterase activity (antialzheimer's activity)

The anticholinesterase activity of *Achillea fragrantissima* was assessed *in vitro*. Depending on the solvent type, the ethyl acetate fraction showed the highest inhibitory effect on acetylcholinesterase (AChE). In contrast, the hydro-alcoholic fraction expressed the highest inhibitory activity on butyryl-cholinesterase (BChE). The study findings highlighted possible applications of *A. fragrantissima* flower extracts as adjuvant therapy in Alzheimer's disease management [132].

The volatile oil and the aqueous, ethyl acetate, and chloroform extracts of *Schinus molle* were assayed for their inhibitory effect against acetylcholinesterase (AChE) and butyryl-cholinesterase (BChE). Most of the extracts revealed moderate to strong inhibitory activities, and the chloroform extract showed the strongest inhibitory activity against both enzymes compared to Tacrine. The leaves essential oil and the ethyl acetate extract exhibited moderate inhibitory activity, but the fruit essential oil was considered inactive against BChE [133].

3.7.5. Wound healing

The wound-healing activity of fresh crude aerial parts of *Portulaca oleracea* (50 mg) was studied using *Mus musculus* JVI-1. The results showed that *Portulaca oleracea* accelerated the wound-healing process by decreasing the surface area of the wound and increasing the tensile strength [134]. It signifies the maturity and strength of the collagen fibers formed in the area of the incision wound [135]. The hexane extract of *Alkanna strigos* was also found to possess wound-healing properties by improving the tensile strength of incision wounds [135].

It was also demonstrated that the aqueous extracts from the dried aerial parts of *Inula viscosa* supported wound healing, accelerated the repair, and organized the epidermis in the presence of mature scar tissue in the dermis. The capacity of wound healing with the *Inula viscosa* could be explained based on the plants' anti-inflammatory effects, which are well documented in the literature [136]. Another study, *Antirrhinum majushis*, revealed innovative healing power. The flowers' extract ointment (5% w/w) was superior compared to the leaves extract (5% w/w) and the positive-control ointments (MEBO) (1.5% w/w) Moreover, *Schinus molle* aqueous extract was also reported to enhance the fibrosis, neovascularization and re-epithelialization of the epidermis and sub-epidermal cells in the regenerated tissue. In addition, it increased the tensile strength of the skin *in vivo* model [137].

3.7.6. Anti-ulcer

One study reported that the combination of *Punica granatum* extract and metronidazole exhibited a synergistic activity against *H. pylori* with MIC of 0.156 mg/ml [126]. The protective effect of *Anchus strigosa* was also reported using ether and chloroform soluble fraction in ethanol-induced ulcer model in rats [138].

3.7.7. Xanthine oxidase inhibitory activity

Many tested species of Jordanian plants were reported to have good activity in inhibiting xanthine oxidase enzyme, namely *Salvia spinosa* ($IC_{50} = 0.053$ mg/ml), *Anthemis palestina* (0.168 mg/ml), *Chrysanthemum coronarium* (0.199 mg/ml), *Achillea biebersteinii* (0.36 mg/ml), and *Rosmarinus officinalis* (0.65 mg/ml) [130].

3.7.8. Sleep deprivation-induced memory impairments

Chronic sleep deprivation is well known to impair short- and long-term memory formation. Treatment of animals with *Arbutus andrachne* fruit extract was reported to prevent long-term and short-term memory impairment at specific doses. Moreover, *Arbutus andrachne* fruit extract normalized the reduction in the hippocampus GSH/GSSG ratio and activity of GPx, and catalase. This effect is probably due to normalizing oxidative stress in the hippocampus [139].

4. Limitations

The findings of this study gave an indicative impression of the Jordanian medicinal flora. However, this review included only 124 studies that met the inclusion criteria. Which merely comprises a limited number of the 2543 Jordan's medicinal plant. Furthermore, despite efforts made to include all related articles in the literature. Non-English articles could not be included in this review.

5. Conclusions and perspectives

The current review gathered the data from several research articles that clearly showed the important of medicinal herbs and plants in the treatment of several diseases including cancer, diabetes, and infectious disease. The review provided an account of the studies conducted for plants growing and used traditionally for treating several diseases in Jordan using *in vitro* and *in vivo* models emphasizing the therapeutic potentials of these species. Medicinal plants are the only natural resource for developing effective, safe, quality drugs.

Therefore, increasing awareness and investigation of phytochemicals of plants of Jordanian flora and the need for further scientific evaluation should be considered as a national priority. This review can give researchers opportunities for using this heritage in exploring new agents to treat several diseases. And help in discovering false medicinal herbs use. In addition, further screening and investigation are required regarding their phytochemicals, mechanism of action and safety profile. Studying active phytochemicals for disease treatment will help develop drugs for safe treatment and cure in the future.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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