Saudi Arabian Plants: A Powerful Weapon against a Plethora of Diseases

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Abstract: The kingdom of Saudi Arabia (SA) ranks fifth in Asia in terms of area. It features broad biodiversity, including interesting flora, and was the historical origin of Islam. It is endowed with a large variety of plants, including many herbs, shrubs, and trees. Many of these plants have a long history of use in traditional medicine. The aim of this review is to evaluate the present knowledge on the plants growing in SA regarding their pharmacological and biological activities and the identification of their bioactive compounds to determine which plants could be of interest for further studies. A systematic summary of the plants' history, distribution, various pharmacological activities, bioactive compounds, and clinical trials are presented in this paper to facilitate future exploration of their therapeutic potential. The literature was obtained from several scientific search engines, including Sci-Finder, PubMed, Web of Science, Google Scholar, Scopus, MDPI, Wiley publications, and Springer Link. Plant names and their synonyms were validated by "The Plant List" on 1 October 2021. SA is home to approximately 2247 plant species, including native and introduced plants that belong to 142 families and 837 genera. It shares the flora of three continents, with many unique features due to its extreme climate and geographical and geological conditions. As plants remain the leading supplier of new therapeutic agents to treat various ailments, Saudi Arabian plants may play a significant role in the fight against cancer, inflammation, and antibiotic-resistant bacteria. To date, 102 active compounds have been identified in plants from different sites in SA. Plants from the western and southwestern regions have been evaluated for various biological activities, including antioxidant, anti-cancer, antimicrobial, antimalarial, anti-inflammatory, anti-glycation, and cytotoxic activities. The aerial parts of the plants, especially the leaves, have yielded most of the bioactive compounds. Most bioactivity tests involve in vitro assessments for the inhibition of the growth of tumour cell lines, and several compounds with in vitro antitumour activity have been...
reported. More in-depth studies to evaluate the mode of action of the compounds are necessary to pave the way for clinical trials. Ecological and taxonomical studies are needed to evaluate the flora of SA, and a plan for the conservation of wild plants should be implemented, including the management of the protection of endemic plants.

**Keywords:** Saudi Arabian plants; distribution; anti-inflammation; anti-cancer; antibiotic resistance; active compounds

1. Introduction

The plants of Saudi Arabia (SA) have high biological diversity in the Arabian Peninsula, where they represent an important genetic resource for crop and medicinal plants. About 30% of these plants are rare due to the geographical location and dry weather characteristics of SA [1,2]. Various parts of the plants are used in traditional medicine, including the bark, flowers, fruits, leaves, resins, rhizomes, roots, seeds, and stems. All plants contain primary metabolites, while secondary metabolites serve a specific plant species in the interaction with its environment. The contents of biologically active compounds are plant-specific and genetically determined; however, they are also affected by the cultivation, practices, pests and diseases, climate, weather, stage of development (season, young and old leaves), ecosystem, and the time of the day the material is collected [3]. Because of the extreme conditions in SA, plants have developed different strategies to survive. In terms of phytochemistry, this results in high levels of secondary metabolites, such as flavonoids, polyphenols, terpenes, tannins, saponins, sterols, alkaloids, and their glycosides [3].

The importance of natural products for novel drug development is obvious from present-day pharmacology, and many natural products have served as the basis for developing medicines and are still used as medicines for various ailments. Morphine and codeine from *Papaver somniferum* L., quinidine, and quinine from *Cinchona* spp., atropine from *Atropa belladonna* L., and digoxin from *Digitalis* spp. are prominent examples of well-established plant-derived pharmaceutical preparations [4]. Newman and Cragg [5] demonstrated that almost one-half of all novel medicines developed in recent decades are natural products or natural product derivatives and analogues. Therefore, searching nature for novel hits for the development of medicine is increasing [6].

Novel medicines are required because of several problems with present-day pharmaceuticals, including severe side effects and resistance to anti-cancer medicines or antibiotics. For example, the common non-steroidal anti-inflammatory drugs (NSAIDs) are known for their side effects, such as cardiovascular incidents and gastrointestinal bleeding [7]. A recent study conducted in SA reported that the side effects of NSAIDs and antibiotics were reported by 80.7% (*n* = 272) and 48.7% (*n* = 164) of users, respectively [8]. Novel NSAIDs with fewer side effects are needed. In addition to the side effects of antibiotics, their uncontrolled use increases the likelihood of microorganisms developing resistance, and thus, increases the number of severe infections and mortality [9]. Cancer incidence in SA has increased in the past 27 years; thyroid cancer incidence increased by 26-fold and breast, bladder, colon, and uterine cancer incidences increased by about 10-fold. The number of cancer deaths in SA increased from 5% in 1990 to 12% in 2016 [10].

Saudi citizens are dependent on both traditional medicinal plants and modern medicines, as was reported in a review on the ethnopharmacology of SA plants [11]. Although several publications report on traditional medicines in SA [12–14], there is no comprehensive review about the total plant biodiversity in SA and its uses to date. Combining traditional knowledge with modern pharmacognostic research, novel hits for drug development may be found, resulting in the evidence-based use of traditional medicines. Other recent studies have shown interesting non-medical applications of secondary metabolites from Saudi Arabian plants. An example of a plant from SA with a high content of valuable...
compound(s) is *Plectranthus aegyptiacus*, a source of thymol, which is the main component of the plant’s essential oil (58.49%). Thymol is a volatile phenolic monoterpenoid; among other uses, it is used in food conservation [15–18].

The aim of this review is to evaluate the present knowledge on the plants growing in SA regarding their pharmacological and biological activities and the identification of bioactive compounds. A critical analysis of the published evidence should lead to the identification of plant species that are of interest for further studies of biologically active compounds. This could lead to the evidence-based application of traditional medicines and novel leads for drug development. Furthermore, other non-medical applications of SA plants and their constituents may result from the present knowledge. Therefore, this review should serve as the basis for selecting plants for further in-depth reviews of the active compounds previously reported in plants growing outside SA or plant compounds that have been previously isolated from other sources. A major effort to study biodiversity in SA was recently made by Alqethami et al. [3]. In their phytochemical screening of 85 different medicinal plant species used in Jeddah city for traditional medicine, glycosides (82%; 70 species) were the most common followed by tannins (68%; 58 species), alkaloids (56%; 48 species), saponins (52%; 44 species), and flavonoids (35%; 30 species) [3].

As part of our ongoing project on chemical and pharmacological studies of plants used in traditional medicine [19,20], in this review, we will focus on the NSAIDs, antibiotics, and antitumour compounds that have been reported in plants growing in SA. Cardiovascular disease, diabetes, and obesity targets deserve more attention.

2. Distribution and Diversity of the Flora of Saudi Arabia

SA is the largest country in the Arabian Peninsula, occupying about 2.25 million km², or nearly 80% of the peninsula [21]. Forests cover about 27,000 km² of its total area, mostly in the southwestern part of the Kingdom [22], while the area of natural rangeland exceeds 1.75 million km² [23]. Plant diversity plays a key role in maintaining and preserving ecological balance and stability, which is an important factor for human well-being, not only for the country but for the whole world [24]. In recent years, a significant amount of data have been published about the flora in SA, which revealed that the country is gifted with a wide variety of plants, including a large number of herbs, shrubs, and trees that are found in desert, semi-desert, and mountainous ecosystems [25–27]. Geographic and climatic diversity, changes in water resources, drought, and anthropogenic pressures, such as overgrazing, deforestation, and all developmental activities in SA, negatively affect biodiversity, impacting the structure of the flora and natural vegetation [22,28]. The climate of SA varies greatly depending on the area and the season; it is characterised by extremes in weather, with very high temperatures during the daytime followed by an abrupt drop in temperature at night and very little, irregular precipitation (i.e., a typical ‘desert climate’) [21]. The annual mean temperature of the country is 24.64 °C, with Turaiif in the north recording the lowest temperature (19.10 °C) and Makkah in the west recording the highest temperature (31.69 °C), with an average of 17.62 °C, exhibiting an increasing gradient from north to south [29]. Rainfall and temperature are considered the key controllers of agricultural production [30]. The annual average rainfall in SA from 1979 to 2009 was 93.5 mm, and it is expected that by 2050, some parts of SA will experience a decrease in rainfall by 20–25% in dry seasons and 10–15% in the winter. The maximum temperature has increased significantly, especially in dry seasons, by 0.72 °C per decade [31].

SA is home to about 2,247 plant species, including native and introduced plants that belong to 142 families and 837 genera, and the components of its flora are the admixture of the features of Africa, Asia, and the Mediterranean region in addition to a large number of about 246 endemic species [32–36]. Of them, about 105 species reside in dunes, 90 species are halophytes, 75 species are trees, and aquatic plants comprise 12 species. About 450 species of total flora have a direct benefit to humans; 334 species have medicinal value, 38 species are palatable fodder, 25 species are human food, 45 species are poisonous, 47
species are used as ornamentals, and 471 species are used in ethnomedicine [22,37]. Of note, about 600 species of plants in SA are rare and endangered in their habitat [38].

Mecca city district is characterised by various types of plants; it was reported that a total number of 184 species of 125 genera and 44 families are found in Mecca. The most well-known families are Poaceae (17%), Fabaceae (13%), and Amaranthaceae (5%) [32]. Moreover, wadis represent one of the most notable desert landforms where physiographic irregularities appear, leading to parallel variation in species distribution and life forms. In wadi Al-Noman in Mecca, about 126 species from 39 families have been recorded, namely Fabaceae, Poaceae, and Boraginaceae. The authors indicated that species diversity in the studied area may be positively associated with the high pH and mineral content of the soil [39]. The vegetation along a transect between Makkah Al-Mukarramah and Al-Madina Al-Munawarah in the Hejaz Mountains includes 106 species of vascular plants from 35 families [40]. In a survey of a sector in the Hejaz mountains along the Medina-Badr road, 247 species of 173 genera and 52 families are listed [41]. In Jizan province in the southern region, with varied landscapes such as wadis, islands, plateaus, and mountains, 850 species of 434 genera from 98 families represent about 37% of all the species in SA. Of them, 536 species are from Jabal Fayfa and 202 species are from the Farasan Islands. The most dominant families are Poaceae, Papilionaceae, and Asteraceae, with a total of 87, 70, and 60 species, respectively [42]. In a survey of the flora of the Sarwat Mountains in Taif as showed in Figure 1, 261 species from 178 genera and 55 families were recorded, of which Asteraceae, Poaceae, Fabaceae, Lamiaceae, Chenopodiaceae, Boraginaceae, Asclepiadaceae, Brassicaceae, and Zygophyllaceae were the most common [43]. In another mountainous area, the Asir mountains in the southwest of SA, 189 species of 74 families were recorded; Asteraceae was the dominating family in the study area (36.5%) followed by hemicryptophytes (15%) and geophytes (12.5%) [28]. In the eastern part of the Kingdom, no more than 370 native species of herbs and shrubs are adapted to the desert climate, reflecting the difficulties faced by plants in these harsh environments; the same applies for the northern part [44]. This is in contrast with Asir Hijaz, the western mountainous area of the Kingdom, which has large species diversity due to the greater rainfall [33]. The number of recorded species is still increasing through new biodiversity surveys [32]; however, the richness and diversity of the flora might be lost due to anthropogenic pressure and changes in climate [37,45]. Therefore, further studies are needed to ecologically and taxonomically evaluate all the flora of the country and to provide suitable conservation measures for these valuable species with unique features.
3. History of Medicinal Plants in Saudi Arabia

People have used plants to meet their various needs throughout different eras. Plants have formed the basis of traditional medicine for at least 6000 years in Mesopotamia and Egypt, with Hippocrates serving as a landmark for the written traditions on medicines [46,47]. Traditional medicine has been and is still a part of the culture of SA [48]. SA has some unique features besides its religious position. Zamzam Well is one of the most well-known places in SA, known for its suitable environment for many herbs and shrubs, as mentioned in the verses of the Qur’ân:

“Our Lord, I have settled some of my offspring in a barren valley, near your sacred House, our Lord, that they may establish prayer. So make the hearts of people incline towards them and provide them with sustenance that they may give thanks” (Verse # 37, Surah Ibrahim, p. 260).

Agriculture has been the main source of economic income for several Saudi regions, even during the pre-Islamic times, and farmers followed both advanced and traditional irrigation methods by diverting rainwater flowing into agricultural terraces or bringing rainwater drawn from dams to irrigate parched wadis [43]. From the 7th century, SA has been the historical origin of Islam. ‘Traditional Islamic medicine’ is the term used to describe medical traditions thriving during Islam’s golden age [49]. In fact, many plants are highly recommended by Prophet Muhammad (peace be upon him (PBUH)). Other plants are mentioned in different surahs of the Holy Qur’ân, such as date palm, olive, toothbrush tree, camphor tree, squash, ginger, onion, grapes, clover [50]. Prophet Muhammad (PBUH) mentioned the use of Miswak (Salvadora persica L.) for oral hygiene [51]. The Prophet (PBUH) said, ‘Siwak (Miswak) is a means of purification for the mouth and is pleasing to the Lord’ [52]. At that time, the use of medicinal plants to prevent and treat health disorders flourished, and philosophers and physicians, such as Al-Razi and Ibn Sina, began to change the concept of medicine. They compiled medical books from the knowledge available in the Mediterranean region (e.g., from Egyptian, Persian, Greek, and Roman times) that have been used for centuries (700–1500 AD). This knowledge was selected through controlled experimentation and sound reasoning. ‘The Canon of Medicine’, ‘The Book of Healing’, and ‘Kitab Al-Hawi’ are the most famous books written by Ibn Sina (Father of Early Modern Medicine) and Al-Razi [50,53].
For these reasons, people in SA have taken an interest in plants; about 80% of Saudi citizens have used medicinal plants for their primary health care [11]. Recent publications reported the activity of S. persica (Miswak, toothbrush tree) against oral bacteria that cause caries. This species showed effective antimicrobial, antiulcer, analgesic, anti-inflammatory, and antitumour activities, which agrees with the recommendations of the Prophet (PBUH) [54]. The uses of 12 medicinal plants that were recommended by the Prophet (PBUH) and mentioned in Qur’anic verses were recently published [50,55].

4. Anti-Inflammatory Activity of Saudi Arabian Plants

People have always been exposed to inflammatory diseases; the clinical symptoms were first described by the Roman physician Cornelius Celsus in the first century A.D. [56]. Inflammation is an immune response to various external factors, such as infection with microorganisms, toxic compounds, damaged cells, or irradiation [57]. An inflammatory response is a multi-step process initiated by inducers that are detected by specific receptors (sensors) on specialised sentinel cells (e.g., mast cells, macrophages, and dendritic cells). Sensors stimulate the production of mediators, such as cytokines, chemokines, eicosanoids, bioactive amines, and products of proteolytic cascades, which affect target tissues [56]. Such inflammatory inducers may lead to acute and/or chronic inflammatory responses in various body organs (e.g., liver, heart, brain, lung, intestinal tract, kidney, pancreas, and reproductive system), resulting in tissue damage or disease [58,59]. Worldwide, three out of five people die due to chronic inflammation caused by cardiovascular diseases, cancer, stroke, bowel diseases, chronic respiratory diseases, arthritis, obesity, and diabetes [60]. Unfortunately, the available anti-inflammatory drugs are associated with a number of side effects, including cardiovascular effects and gastrointestinal bleeding [7]. Therefore, there is a need for new potent drugs with fewer side effects for better management of inflammatory ailments. Natural products, especially medicinal plants, are a rich source of phytochemicals, which have been shown to relieve pain or have anti-inflammatory effects [61–63]. For example, curcumin isolated from Curcuma longa L. was the subject of several clinical studies of inflammatory diseases [64]. In-depth studies are needed to identify the mode of action and to optimise the pharmacological profile of plant extracts and active compounds.

Regarding the native plants of SA, several have been found to inhibit either the production of pro-inflammatory mediators or decrease their action, leading to anti-inflammatory activity [65]. Essential oils from Achillea fragrantissima Sch. Bip. and Lactuca serriola L., two plants of the family Asteraceae that grow in SA, were investigated for their anti-inflammatory activity; they were shown to exhibit a high inhibition of carrageenan-induced oedema after 4 h at a dose of 100 mg/kg orally by 71.9% and 73.4%, respectively [66]. The promising effects were due to the presence of azulene and oxazolidine in both A. fragrantissima and L. serriola [66]. Elsharkawy et al. [67] examined the anti-inflammatory effects of a mixture of three different plants (Artemisia herba alba, Rubia tinctorum, and Alkanna tinctoria) used by Bedouins in SA to treat many skin diseases. The oil mixture of these plants showed anti-inflammatory activity with oedema inhibition after 4 h (78.0% with 100 mg/kg orally) compared to the standard drug (89.5% with 10 mg/kg indomethacin) [67]. Using a bioassay-guided approach to identify the anti-inflammatory activity of compounds in Cadaba glandulosa Forssk, four active compounds were isolated and identified. The paw oedema thickness of rats was found to be 3.04, 3.11, 4.16, and 4.89 mm 4 h after the application of compounds 3, 2, 1, and 4, respectively, at 10 mg/kg subcutaneously compared with the standard drug (indomethacin 10 mg/kg reduced oedema thickness to 4.47 mm) [68]. Regarding the structure–activity relationship (SAR), compound 3 exhibited the highest anti-inflammatory activity in this study. The total MeOH extract (100 mg/kg) of C. glandulosa Forssk reduced the oedema thickness to 4.29 mm after 4 h [68]. Six triterpenes (compounds 5–10) of Kleinea odorata were evaluated for their anti-inflammatory activity, causing a decrease in pro-inflammatory genes like nuclear transcription factor-kB (NF-κB) and cascaded interleukins (IL-6, IL-1β, and TNF-α) [69]. Only compounds 5 and 6
produced a notable change, decreasing oedema thickness at a low dose of 0.4 μg/mL, but other compounds (7–10) showed only good anti-inflammatory activity at 40 μg/mL. Regarding skin SAR, the activity may be due to the lupane nucleus with ketone or acetate at position C-3, as in compounds 6 and 5 in Figure 2, respectively; however, the presence of an OH group at position 3 causes a decrease in activity, as for compounds 8 and 9 [69]. Hexane and chloroform extracts of \textit{Hueinia} Sp. Nov. aff. Boleana exhibited good activity, as the rats’ tail volume decreased and wound repair and re-epithelisation were enhanced [70]. Additional plants and active compounds with potent anti-inflammatory activity from the central and western regions of SA have been reported (Table 1).

![Figure 2. Structure of compounds 1 to 10 with anti-inflammatory effects.](image)

**Table 1.** The biological activities of isolated compounds from plants in the central and western regions of SA.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Plant/Family</th>
<th>Location/Time</th>
<th>Solvent/Part Used</th>
<th>Animal, Cell Line, Organism, or Method Used</th>
<th>Activity</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>\textit{Premna resinos}a (Hochst.) Schauer/Lamiaceae</td>
<td>Riyadh (central)/Jan. 2011 region</td>
<td>Methanol extract/aerial parts</td>
<td>Daoy, HepG2, and SK-MEL28/DPPH Scavenging activity (DPPH SCA) assay</td>
<td>Cytotoxic activity just against Daoy cell line with IC$_{50}$ = 10.5 μg/mL PC = 7.3 μg/mL</td>
<td>[71]</td>
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<td></td>
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<td>Antioxidant activity via inhibition of the discoloration of β-carotene by 94.4% at 1000 μg/mL PC = 93.1%</td>
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<td></td>
<td>\textit{Commiphora opobalsamum}</td>
<td>Near Abha city (Southern)/2003</td>
<td>Various fractions/aerial parts</td>
<td>DCFH-DA method/HL-60 cells</td>
<td>Antioxidant activity with IC$_{50}$ = 0.55 μg/mL PC = 0.39 μg/mL</td>
<td>[72]</td>
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<tr>
<td>Line</td>
<td>Plant Species</td>
<td>Geographical Location</td>
<td>Method of Preparation</td>
<td>Assay</td>
<td>Activity Type</td>
<td>Results</td>
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<td>24</td>
<td><em>P. resinosa</em> (Hochst.)</td>
<td>Riyadh (central) Jan. 2011</td>
<td>Methanol extract/aerial parts</td>
<td>HepG2, Daoy, and SK-MEL28/DPPH SCA assay</td>
<td>Cytotoxic activity just against Daoy cell line with IC₅₀ = 21.1 μg/mL</td>
<td>PC = 7.3 μg/mL</td>
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<td>Antioxidant activity via inhibition of the discoloration of β-carotene by 91.2% at 1000 μg/mL</td>
<td>PC = 93.1%</td>
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<td>25</td>
<td><em>P. resinosa</em> (Hochst.)</td>
<td>Riyadh (central) Jan. 2011</td>
<td>Methanol extract/aerial parts</td>
<td>HepG2, Daoy, and SK-MEL28/DPPH SCA assay</td>
<td>Cytotoxic activity just against Daoy cell line with IC₅₀ = 7 μg/mL</td>
<td>PC = 7.3 μg/mL</td>
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<td>Antioxidant activity via inhibition of the discoloration of β-carotene by 80.9% at 1000 μg/mL</td>
<td>PC = 93.1%</td>
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<td>26</td>
<td><em>P. resinosa</em> (Hochst.)</td>
<td>Riyadh (central) Jan. 2011</td>
<td>Methanol extract/aerial parts</td>
<td>Daoy, HepG2, and SK-MEL28/DPPH SCA assay</td>
<td>Cytotoxic activity just against SK-MEL28 cell line with IC₅₀ = 19.6 μg/mL</td>
<td>PC = 7.3 μg/mL</td>
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<td>Antioxidant activity via inhibition of the discoloration of β-carotene by 90.5% at 1000 μg/mL</td>
<td>PC = 93.1%</td>
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<td><em>P. resinosa</em> (Hochst.)</td>
<td>Riyadh (central) Jan. 2011</td>
<td>Methanol extract/aerial parts</td>
<td>Daoy, HepG2, and SK-MEL28/DPPH SCA assay</td>
<td>Cytotoxic activity just against SK-MEL28 cell line with IC₅₀ = 18.8 μg/mL</td>
<td>PC = 23.8 μg/mL</td>
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<td>Antioxidant activity via inhibition of the discoloration of β-carotene by 86.2% at 1000 μg/mL</td>
<td>PC = 93.1%</td>
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<td>38, 39, 40, 41, 42, 43, 44, 45, 24, and 46</td>
<td>Sisymbrium Najed Region (central) Apr. 2008</td>
<td>Ethanol extract/aerial parts</td>
<td>Scavenging of the ABTS radical</td>
<td></td>
<td>Antioxidant activity ranged from 372 to 785 μM Trolox equivalent/g dry weight</td>
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<td>52, 53, 54, 47, 55, 56, 35, 57, and 58</td>
<td><em>Cordia sinensis</em>/Borraginacea</td>
<td>Riyadh (central)</td>
<td>Methanol extract/dried plant</td>
<td>Carrageen-induced paw oedema of rats</td>
<td>Anti-inflammation-inhibited oedema ranged from 38.4 to 62.4%</td>
<td>PC = 57.6%</td>
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<tr>
<td>68</td>
<td><em>Sarcocornia fruticose</em>/Chenopodiacea</td>
<td>Al-Kharrar lagoon-Red Sea, Jeddah (west) Apr. 2016</td>
<td>Methanol extract/leaves</td>
<td>HCV Protease inhibitory assay</td>
<td>Showed inhibition of HCV protease with IC₅₀ = 8.9 μM</td>
<td>PC = 1.5 μM</td>
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<td>69 and 70</td>
<td><em>S. fruticose</em>/Chenopodiacea</td>
<td>Al-Kharrar lagoon-Red Sea, Jeddah</td>
<td>Methanol extract/leaves</td>
<td>DPPH SCA assay</td>
<td>Antioxidant activity with IC₅₀ = 3.8 and 4.3 μM of compounds 69 and 70, respectively</td>
<td>PC = 1.5 μM</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>No.</th>
<th>Species/Genus</th>
<th>Collection Location</th>
<th>Plant Part</th>
<th>Assay</th>
<th>Activity</th>
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</thead>
<tbody>
<tr>
<td>71</td>
<td><em>P. punctulata</em></td>
<td>Al-Kharrar lagoon-Red Sea, Jeddah (west)/Apr. 2016</td>
<td>Methanol extract/root</td>
<td>Jurkat and HeLa cell lines/</td>
<td>The antiproliferative activity caused growth inhibition with IC_{50} = 12 and 18μM of Jurkat and HeLa cells, respectively, due to inducing cell cycle arrest in G0/G1. Lowering the basal level of peroxides DHFDA-load in the cell.</td>
</tr>
<tr>
<td>73, 74, 75, 23, and 60</td>
<td><em>Cassia italica</em></td>
<td>Gabal Al-Ateeq, Al Madinah Al Munawwarah (west)/Apr. 2017</td>
<td>Ethyl acetate fraction/aerial parts</td>
<td>DPPH assay</td>
<td>Potent antioxidant activity ranges from 19.7 to 95.8%, compared to butylated hydroxyanisole 93.8%</td>
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<tr>
<td>37</td>
<td><em>Psiadia punctulata</em></td>
<td>Wadi Ghazal (west)/Jun. 2012</td>
<td>Dichloromethane surface extract/leaves</td>
<td>Biofilm inhibition against <em>C. Albicans</em> and <em>S. aureus</em></td>
<td>Reduce the biofilm formation of both <em>S. aureus</em> and <em>C. Albicans</em> at 40 μg/mL concentration by 50% and 90%, respectively</td>
</tr>
</tbody>
</table>

PC: positive control.

5. Anti-Cancer Activity of Saudi Arabian Plants

Cancer is an increasing problem, with a high incidence and high rate of mortality. Cancer is a general term for a number of chronic diseases commonly associated with the presence of malignant cells. Cells divide abnormally, with a lack of differentiation, and are unable to respond to normal physiological stimuli, quickly spread to the surrounding tissues [78–80]. Cancer can be caused by internal factors, including gene mutations, hormones, immune disorders, or other cellular changes, and external factors, such as tobacco, diet, infectious diseases, radiation, chemicals, or obesity [81]. According to global statistics, there were about 19.3 million new cancer cases and nearly 10 million deaths from cancer worldwide in 2020 [82,83]. The Saudi Cancer Registry estimated the total number of incident cases of cancer in 2012 to be 14,336 cancer cases, with 6791 among males and 7545 among females. Incidence varied by region, with the East and Riyadh showing the highest age-standardised rates for both males and females, and the lowest was in Hail and Jazan [84]. Breast (14.2%) and colorectal (11.1%) cancers were the most widespread cancers diagnosed in SA in 2012. The projection model predicted a fourfold increase in the incidence of colorectal cancer in SA in both sexes by 2030 [85]. The 10 most common cancers among Saudis are presented in Figure 3 [84].
Numerous conventional and advanced methods are used to treat and aid in cancer control, including radiation therapy, surgery, and chemotherapy. Nowadays, there are novel strategies for cancer control and treatment, including gene therapy, immunotherapy, photodynamic therapy, hyperthermia treatment, and hormone therapy [86,87]. Over 50% of the available anti-cancer drugs are natural products, modified natural products, or synthesised analogues [88–90]. Despite these advanced technologies and the extensive research that has been published recently, cancer remains a worldwide killer [91]. Anti-cancer drugs not only destroy cancer cells but also affect normal cells [92]; therefore, the search for natural products with no or lower side effects is ongoing.

Because plants have wide chemical diversity, their compounds provide a valuable opportunity to discover new drugs [6]. According to Newman and Cragg (2020), around two-thirds of anti-cancer drugs are derived from naturally occurring secondary metabolites [5]. For example, paclitaxel is a vital anti-cancer alkaloid that was isolated for the first time from the bark of the western yew (Taxus brevifolia Nutt.) and was characterised as part of the National Cancer Institute screening programme at the Research Triangle Institute [93].

The Kingdom of SA is rich in plants that have been reported to have anti-cancer and antioxidant activity as in Table 2 [18,37,94]. About 91 plant species from SA belonging to 38 families have exhibited anti-cancer activities against different human cancer cell lines. The plant families that have received the most attention due to their anti-cancer impact are Asteraceae (25%), Apocynaceae (10%), Fabaceae (7%), Boraginaceae (3%), and Brassicaceae (3%) [95]. For example, Catharanthus roseus L., which belongs to the Apocynaceae family, grows throughout in the Kingdom of SA, especially in the Makkah region, and it is known to contain more than 150 valuable alkaloids [96]. Vinblastine and vincristine; two important vinca alkaloids of C. roseus, are used as anti-cancer drugs [97]. The two compounds are used to treat human neoplasms; vinblastine is used to treat Hodgkin’s disease, lymphosarcoma, choriocarcinoma, neuroblastoma, carcinoma of breast, lungs, and other organs, and in acute and chronic leukaemia, while vincristine sulphate (Oncovin) arrests mitosis in metaphase in acute leukaemia in children, including lymphocytic leukaemia, Hodgkin’s disease, Wilkins’s tumour, neuroblastoma, and reticulum cell sarcoma [98]. In another study in which eight sesquiterpene lactones and six methoxylated
flavonoids were isolated from *Artemisia sieberi* Besser (Asteraceae family), a plant growing in SA, the isolated flavonoids exhibited cytotoxic activity against human MCF-7 and HeLa cell lines. Compounds 11, 12, and 13 as in Figure 4 exhibited the highest cytotoxic activity, with $IC_{50}$ = 2.3, 3.9, 4.3 μg/mL, respectively, against HeLa cells and $IC_{50}$ = 4.1, 3.2, 6.9 μg/mL, respectively, against MCF-7 cells (doxorubicin as a control at 0.40 and 0.69 μg/mL) compared with other flavonoids (14–16) [99]. In vitro and in vivo investigations of two compounds isolated from the fruits of *Citrullus colocynthis* L. Schrad. collected from the desert of Makkah, namely cucurbitacin I glucoside (17) and cucurbitacin E glucoside (18), showed strong cytotoxic activity against HepG2 cells with $IC_{50}$ of 1.9 and 2.5 μg/mL, respectively, against MCF-7 cells (doxorubicin as a control at 0.40 and 0.69 μg/mL) compared with other flavonoids (14–16) [99]. In vitro and in vivo investigations of two compounds isolated from the fruits of *Citrullus colocynthis* L. Schrad. collected from the desert of Makkah, namely cucurbitacin I glucoside (17) and cucurbitacin E glucoside (18), showed strong cytotoxic activity against HepG2 cells with $IC_{50}$ of 1.9 and 2.5 μg/mL, respectively, against MCF-7 cells (doxorubicin as a control at 0.40 and 0.69 μg/mL) compared with other flavonoids (14–16) [99].

In addition to these activities, both compounds can prolong life span and survival time and regulate the biochemical parameters in vivo of rats that have Ehrlich’s ascites carcinoma tumours [100]. The methanol extracts of different parts of 11 plants from SA exhibited anti-cancer potential in a human liver cancer cell line, and the most active extracts of *Artemisia monosperma*, *Calligonum comosum*, *Ochradenus baccatus*, and *Pulicaria glutinosa* Jaub. and Spach were analysed to detect the presence of 41 phytomolecules, including the compounds 1-(2-hydroxyphenyl) ethenone, 3-(4-hydroxyphenyl) propionitrile, 8,11-octadecadiynoic acid methyl ester, and 6,7-dimethoxycoumarin, respectively [101]. These plant families may have unique anti-cancer properties. Therefore, other compounds occurring in these plants need in-depth studies to be applied as anti-cancer drugs.

**Table 2.** The biological activities of isolated compounds of plants grown in the southwestern regions of SA.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Plant/Family</th>
<th>Location/Time</th>
<th>Solvent/Part Used</th>
<th>Animal, Cell Line, Organism, or Method Used</th>
<th>Activity</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td><em>Anvillea garcini</em> (Burm.f.) DC./Asteraceae</td>
<td>15 km southwest of Al-Kharj city/Feb. 2016</td>
<td>Ethanol extract/leaves</td>
<td>E. fergusonii, C. albicans, E. xiangfangensis, S. aureus, B. licheniformis, C. parapsilosis, and P. aeruginosa</td>
<td>$MIC_{50}$ = 32.3 and 22.3 mg/mL against C. albicans, and C. parapsilosis $PC = 54.7, 51.5$ mg/mL, respectively $MIC_{50}$ = 0.32, and 1.7 mg/mL against S. aureus and E. fergusonii $PC = 0.523 \mu g/mL$</td>
<td>[102]</td>
</tr>
<tr>
<td>21</td>
<td><em>A. garcinii</em> (Burm.f.) DC./Asteraceae</td>
<td>15 km southwest of Al-Kharj city/Feb. 2016</td>
<td>Ethanol extract/leaves</td>
<td>C. parapsilosis, S. aureus, B. licheniformis, C. albicans, E. fergusonii, E. PC= 54.7, 51.5 mg/mL, respectively</td>
<td>$MIC_{50}$ = 41.6 and 34.9 mg/mL against C. albicans, and C. parapsilosis $MIC_{50}$ = 0.10 and 1.3 mg/mL against S. aureus and E. fergusonii $PC = 0.523 \mu g/mL$</td>
<td>[102]</td>
</tr>
<tr>
<td>27</td>
<td><em>Plectranthus barbatus</em> Andrews/Labiatae</td>
<td>Al-Namas area in Asir (southwest)</td>
<td>Ethanol extract/aerial parts</td>
<td>Hela, HepG2, and HT-29</td>
<td>IC$_{50}$ ranged from 15.10 to 26.58 μg/mL $PC = 6.31-28.19 \mu g/mL$</td>
<td>Antibacterial activity against S. aureus, S. mutans, E. coli, and S. typhi.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>S. aureus, S. mutans, E. coli, and S. typhi.</td>
<td>$MIC_{50} = 31.25 \mu g/mL$ for both $PC = 7.8 \mu g/mL$</td>
<td>Antifungal activity with $MIC_{50} = 64.5 \mu g/mL$ against all except for c. neoformans $31.25 \mu g/mL$ $PC = 1.75-7 \mu g/mL$</td>
</tr>
<tr>
<td>No.</td>
<td>Species</td>
<td>Species Details</td>
<td>Plant Part</td>
<td>Assay</td>
<td>IC₅₀ Ranges</td>
<td>PC Value</td>
</tr>
<tr>
<td>-----</td>
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</tr>
<tr>
<td>28</td>
<td><em>P. barbatus</em> Andrews/Labiatae</td>
<td>Al-Namas area in Asir (southwest)</td>
<td>Ethanol extract/aerial parts</td>
<td>DPPH radical-scavenging activity</td>
<td>Hela, HepG₂, and HT-29</td>
<td>IC₅₀ ranged from 41.23 to 69.55 μg/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Antibacterial activity against <em>S. aureus, S. mutans,</em> and <em>S. typhi.</em></td>
<td>E. coli, <em>S. aureus, S. mutans,</em> and <em>S. typhi.</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Antifungal activity against <em>A. niger, P. aurantiogriseum,</em> <em>C. albicans</em> and <em>C. neoformans</em></td>
<td><em>A. niger, P. aurantiogriseum, C. albicans</em> and <em>C. neoformans</em></td>
</tr>
<tr>
<td>29</td>
<td><em>P. barbatus</em> Andrews/Labiatae</td>
<td>Al-Namas area in Asir (southwest)</td>
<td>Ethanol extract/aerial parts</td>
<td>DPPH SCA assay</td>
<td>Hela, HepG₂, and HT-29</td>
<td>IC₅₀ ranged from 40.72 to 72.75 μg/mL</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Antibacterial activity with MIC= 15.6 μg/mL against all except for <em>E. coli</em></td>
<td><em>E. coli, S. aureus, S. mutans,</em> and <em>S. typhi.</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Antifungal activity with MIC= 15.6–64.5 μg/mL</td>
<td><em>P. aurantiogriseum, A. niger, C. albicans</em> and <em>C. neoformans</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DPPH SCA assay</td>
<td>Total antioxidant activity at 1000 μg/mL</td>
<td>64.8%</td>
</tr>
<tr>
<td>30</td>
<td><em>P. barbatus</em> Andrews/Labiatae</td>
<td>Al-Namas area in Asir (southwest)</td>
<td>Ethanol extract/aerial parts</td>
<td>DPPH SCA assay</td>
<td><em>S. aureus, S. mutans, E. coli,</em> and <em>S. typhi.</em></td>
<td>PC = 3.9–7.8 μg/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Antifungal activity with MIC= ranged from 15.6 to 31.25 μg/mL</td>
<td><em>A. niger, P. aurantiogriseum, C. albicans</em> and <em>C. neoformans</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DPPH SCA assay</td>
<td>Total antioxidant activity at 1,000 μg/mL</td>
<td>64.8%</td>
</tr>
<tr>
<td>34</td>
<td><em>Cadaba farinosa</em> Forssk./Capparidaceae</td>
<td>Al-Baha (southwest)/Mar.2010</td>
<td>Methanol extract/leaves</td>
<td>DPPH SCA assay</td>
<td>Total antioxidant activity by 87.1%</td>
<td>PC = 100%</td>
</tr>
<tr>
<td>35</td>
<td><em>C. farinosa</em> Forssk./Capparidaceae</td>
<td>Al-Baha (southwest)/Mar.2010</td>
<td>Methanol extract/leaves</td>
<td>DPPH SCA assay</td>
<td>Total antioxidant activity by 71.8%</td>
<td>PC = 100%</td>
</tr>
<tr>
<td>36</td>
<td><em>C. farinosa</em> Forssk./Capparidaceae</td>
<td>Al-Baha (southwest)/Mar.2010</td>
<td>Methanol extract/leaves</td>
<td>DPPH SCA assay</td>
<td>Total antioxidant activity by 49.1%</td>
<td>PC = 100%</td>
</tr>
<tr>
<td>62, 63, <em>Tagetes minuta</em> L./Asteraceae</td>
<td>Al-Baha (southwest)/Mar.2015</td>
<td>Methanol extract/aerial parts</td>
<td>DPPH SCA assay</td>
<td>The antioxidant activity showed an 87.13–93.62% scavenging activity at 100 μM.</td>
<td>IL-6 and TNF-α level measurement</td>
<td>[105]</td>
</tr>
</tbody>
</table>
Reduction in NFκB p65, IL-6, and TNF-α levels in PBMCS

<table>
<thead>
<tr>
<th>Plant</th>
<th>Location/Collection Date</th>
<th>Extract/Parts</th>
<th>Cancer Cell Lines</th>
<th>Cytotoxicity</th>
<th>Antibacterial Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Dobera glabra</em> (Forssk)/Salvadoraceae</td>
<td>Shoqaiq (southwest)/Feb. 2013</td>
<td>Ethanol extract/aerial parts</td>
<td>PC-3, HepG-2, and HCT-116</td>
<td>High cytotoxicity against all cell lines with IC_{50} = 8 μg/mL [106]</td>
<td></td>
</tr>
<tr>
<td><em>Euphorbia schimperi-ana</em>/Euphorbiaceae</td>
<td>Al-Sawda in Asir region (southwest)/Feb. 2018</td>
<td>Ethyl acetate and n-butanol/aerial parts</td>
<td>Listeria monocytogenes, Scott A, <em>S. aureus</em> (ATCC 6538), <em>B. cereus</em>, <em>E. faecalis</em>, <em>S. enterica</em>, <em>P. aeruginosa</em>, <em>K. pneumonia</em>, and <em>E. coli</em> (ATCC 8739)</td>
<td>Compound 84 showed potent cytotoxic activity against PC3 with IC_{50} = 5.5 μg/mL</td>
<td>Compounds 83, 85 and 86 exhibited antibacterial activity against all tested strains [107]</td>
</tr>
</tbody>
</table>

PC: positive control.

Figure 4. Structures of compounds 11–18 with anti-cancer activity.

6. Antibacterial Activity of Saudi Arabian Plants and Their Potential Contribution against Bacterial Antibiotic Resistance

Over a million years, microbes have been present on this planet—developing, surviving, and adapting to environmental changes throughout the eras and causing many infectious diseases [108]. With the discovery of antibiotics 70 years ago, innumerable human lives have been saved [109]. Antibiotics can kill or inhibit the growth of bacteria through various mechanisms (e.g., by inhibiting the final crosslinking stage of cell wall synthesis and forming an irreversible covalent bond with enzymes, resulting in cell wall weakening and cell death) [110]. In addition, antibiotics can act through the inhibition of nucleic acid (DNA and RNA) synthesis, protein synthesis, or disruption of cell membrane function [110, 111]. Through the overuse of antibiotics, bacteria have acquired resistance via mutations, biofilm formation, target protection, or acquisition of inherent genes, such as β-lactams, fluoroquinolones, and aminoglycosides. Moreover, bacteria can convert antibiotics to their inactive forms via hydrolysis or via the addition of chemical groups using enzymes, leading to the dramatic emergence of multidrug-resistant pathogens and the rapid spread of new infections [111–114]. In the U.S. in August 2016, the first case was reported where a patient with an infection caused by *Klebsiella pneumoniae* was resistant to 26 antibiotics, including all aminoglycosides and polymyxins tested, and was
intermediately resistant to tigecycline, resulting in the death of the patient [115]. The most pathogenic bacteria that threaten human health are Enterococcus faecium, Staphylococcus aureus, K. pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species termed the 'ESKAPE pathogens' [116]. These microorganisms are usually associated with an increased economic burden compared with those that are sensitive or have no potential to infect or colonise humans [117]. If there is no action today, there will be no treatment tomorrow, as the dramatic increase in drug resistance without a solution will result in one person dying every 3 s from antibiotic resistance by 2050 [118]. Consequently, pharmaceutical and scientific communities are searching for alternative sources, and natural antimicrobial plant-derived substances will be a powerful weapon against pathogens. Plants are a significant sources of secondary metabolites with antimicrobial properties, such as saponins, terpenoids, alkaloids, tannins, alkenyl phenols, flavonoids, glycosides, sesquiterpenes lactones, and phorbol esters, which help to inhibit and slow the development of resistance in addition to their other activities [119–123]. Unfortunately, only a few new antimicrobials have been reported out of an estimated 250,000 to 500,000 plant species on Earth [114]. Recently, it was reported that 48.7% of people use antibiotics in SA, making it the second most used drug in SA [8]. More seriously, most consumers purchase antibiotics without prescription. For example, in Riyadh city, three-quarters of the examined pharmacies have sold antibiotics without a prescription to consumers, which has greatly affected patients and caused increase in resistant organisms [124]. However, in April 2018, the Ministry of Health in SA banned the purchase of antibiotics without a prescription [125]. Some plant extracts and isolated active compounds act to combat microbial resistance through different mechanisms as showed in Figure 5. For example, Nigella sativa ethanolic extract showed promising results against 99 strains of methicillin-resistant S. aureus at 4 mg/disc concentration, with MIC 0.2–0.5 mg/mL [121,126]. In addition, active compounds from Psiadia punctulata surface extract have antimicrobial activity, with the ability to reduce the biofilm formation of Candida albicans and S. aureus by 90% and 50%, respectively, at a concentration of 40 μg/mL [77]. Recently, Biharee et al. reported the importance of flavonoids as antimicrobial agents, as they impair bacterial efflux pumps, inhibit biofilm formation, disrupt the cell membrane, and prevent cell envelope formation [127]. For example, when the total content of flavonoids of 16 cultivars of dates that are grown in SA were analysed, their content varied from 27 to 199 mg CE/100 g dry weight (DW) [128]. This indicates the potentially potent antibacterial activity against impenem-resistant P. aeruginosa of flavonoid glycosides isolated from Phoenix dactylifera L. (Tamar). All 12 tested strains were sensitive to the flavonoid glycosides at MIC and MBC values of 0.5–1 mg/mL. Scanning electron microscopy revealed that cell morphology was distorted after 60 min of flavonoid glycoside treatment, explained as a result of damage to the P. aeruginosa cell wall and the formation of pores. Moreover, flavonoid glycosides inhibited biofilm formation after 1 h of exposure. According to the authors, the possible mode of action is associated with the distribution of the phospholipid bilayers in the bacterial cell membrane [129]. In another study, the methanol extract of fruits, aerial parts, leaves, and resins of 17 plants were evaluated for their antimicrobial activity; Chenopodium murale L., Commiphora myrrha, Euphorbia helioscopia L., and Solanum incanum L. had MICs of 2.5 mg/mL against Staphylococcus carnosus and Escherichia coli (standard = 0.01 mg/mL) [130]. Aqueous, methyl alcohol, and methanol extracts of S. persica L. from different regions in SA were evaluated for their activity against various organisms, such as S. aureus, Lactobacillus acidophilus, Streptococcus mutans, P. aeruginosa, Fusobacterium nucleatum, Lactobacillus casei, Staphylococcus epidermidis, and Streptococcus salivarius. Their inhibition zones ranged from 9.2 to 29 mm compared with the positive control (15.4–34.0 mm). The potent activity was related to the active components of S. persica, including flavonoids, salvadorine, alkaloids, cyanogenic, salvadourea, glycosides, and tannins, which are known to possess strong antimicrobial activity [131–133]. Methanolic extracts from the leaves, stem, flower, and fruit of Conocarpus erectus L. and the leaves of Aerva javanica exhibited strong antibacterial activity against Bacillus subtilis, S. aureus, and the acid-fast bacterium Mycobacterium
Furthermore, the methanolic extracts of Mentha × piperita and Mentha longifolia populations grown in northern SA showed that M. × piperita contained the flavonoids naringin 328.8 mg/100 g DW, cyanoside 162.8 mg/100 g DW, and higher phenolic acid content than M. longifolia: rosmarinic acid 1547.6 mg/100 g DW, cryptochlorogenic acid 91.7 mg/100 g DW, and chlorogenic acid 69.4 mg/100 g DW. The two Mentha species had potent antioxidant, anti-cancer, and antimicrobial activities attributed to their polyphenols [137,138]. Carvacrol (the main compound in both the volatile oil and aqueous distillates of aerial parts of Origanum vulgare) inhibited the growth of E. coli at 200 µg/mL with an IC₅₀ of 42 µg/mL compared with the control (20 µg/mL), causing cell membrane damage and cell death [139]. Ethanolic extract of various parts of Syzygium aromaticum, Punica granatum, Thymus vulgaris, Cuminum cyminum, and Zingiber officinale exhibited superior activity against bacterial strains that cause diseases of food poisoning [140]. Moreover, it was revealed that the essential oils of Artemisia species (A. absinthium, A. sieberi, and A. scoparia) contain four common compounds: limonene, camphor, terpinen-4-ol, and ethyl 2-methylbutyrate. Artemisia species exhibited good antimicrobial activity against S. aureus CP011526.1, Bacillus licheniformis KX785171.1, and Micrococcus luteus NCTC 2665 bacterial strains and C. albicans MF942350, Candida parapsilosis MF942354, and Aspergillus parasiticus CBS 100926 fungal strains, with MICs ranging from 0.1 µg/mL to 11.0 µg/mL [141]. Methanolic extracts of Pimpinella anisum, Curcuma longa, Zingiber officinale, and Commiphora molmol exhibited significantly higher antimicrobial activity than aqueous extracts when compared with kanamycin as a positive control [142] in addition to other active compounds with potent activity, as illustrated in Table 3. Although SA is home to numerous wild plant species with significant antibacterial activity, few studies have addressed the mechanisms and modes of their action. Therefore, there is a need for in-depth studies to validate the importance of these plant species as antimicrobial agents.

Table 3. The biological activities of isolated compounds from plants in various regions of SA.

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Plant/Family</th>
<th>Location/Time</th>
<th>Solvent/Part Used</th>
<th>Animal, Cell Line, Organism, or Method Used</th>
<th>Activity</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>Origanum vulgare L./Lamiaceae.</td>
<td>Al-Kharj (southeast)/Mar. 2013</td>
<td>Oils/aerial parts</td>
<td>E. coli, M. luteus, P. aeruginosa, and S. aureus</td>
<td>Carvacrol completely inhibited the growth of E. coli at 200 µg/mL⁻¹ with IC₅₀ = 42 µg/mL, PC = 20 µg/mL</td>
<td>[139]</td>
</tr>
<tr>
<td>22</td>
<td>Myrtus communis Linn./Myrtaceae</td>
<td>District Sawat (northwest)/Jul. to Aug. 2016</td>
<td>Acetone extract/leaves</td>
<td>E. coli and S. aureus</td>
<td>Inhibition zone (IZ) of the compound = 36, and 37.5 mm compared to acetone extract, 16.5 mm against E. coli and S. aureus, respectively, at 50 mg/mL</td>
<td>[143]</td>
</tr>
<tr>
<td>31</td>
<td>Commiphora opobalsamum L./Burseraceae</td>
<td>Near Abha city (southern)/2003</td>
<td>Various fractions/aerial parts</td>
<td>Chloroquin-sensitive (D6) and chloroquin-resistant (W2) (strains of P. falciparum).</td>
<td>Antimalarial activity with IC₅₀ = 3.5 and 3.2 µg/mL against D6 and W2 respectively, PC = 9, and 10.5 ng/mL</td>
<td>[72]</td>
</tr>
<tr>
<td>32</td>
<td>C. opobalsamum L./Burseraceae</td>
<td>Near Abha city (southern)/2003</td>
<td>Various fractions/aerial parts</td>
<td>DCFH-DA method/HL-60 cells</td>
<td>Antioxidant activity with IC₅₀ = 5.00 µg/mL, PC = 0.39 µg/mL</td>
<td>[72]</td>
</tr>
<tr>
<td>33</td>
<td>C. opobalsamum L./Burseraceae</td>
<td>Near Abha city (southern)/2003</td>
<td>Various fractions/aerial parts</td>
<td>DCFH-DA method/HL-60 cells</td>
<td>Antioxidant activity with IC₅₀ = 0.70 µg/mL, PC = 0.39 µg/mL</td>
<td>[72]</td>
</tr>
<tr>
<td>47</td>
<td>Gastrocotyle hispida/Boraginaceae</td>
<td>Hail (northwest)/Mar. 2015</td>
<td>Methanol extract/aerial parts</td>
<td>DPPH SCA assay</td>
<td>Antioxidant activity with IC₅₀ = 10.2 µg/mL, PC = 8.1 µg/mL</td>
<td>[144]</td>
</tr>
<tr>
<td>48</td>
<td>G. hispida/Boraginaceae</td>
<td>Hail (northwest)/Mar. 2015</td>
<td>Methanol extract/aerial parts</td>
<td>DPPH SCA assay</td>
<td>Antioxidant activity with IC₅₀ = 52 µg/mL, PC = 8.1 µg/mL</td>
<td>[144]</td>
</tr>
</tbody>
</table>

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| 49, 50, and 51 | G. hispida/Bo-raginaceae | Hail (north-west)/Mar. 2015 | Methanol extract/aerial parts | MDA-MB 231, HEK-293, CF-7, and HepG2 | Anticancer activity against HEK-293, and MCF-7 with IC<sub>50</sub> = 2.3 and 6.2 μg/mL, PC = (3.2–2.4) μg/mL | [144] |
| 59, 40, 60, and 61 | Chrozophora tinctoria/Euphorbiaceae | Al-Hadda road/Apr. 2012 | Methanol extract/aerial parts | Measurement of TNF-α, PGE<sub>2</sub>, IL-1b, IL-6, and levels | Anti-inflammation activity by decreasing the level of IL-1b, IL6, PGE<sub>2</sub>, and TNF-α in the supernatant media of human peripheral blood mononuclear cells (PBMCs) | [92] |
| 76, 77, 78, 79, and 80 | Deverra tortuosa (Desf.)/Apiaceae | Wadi Abalkour (north)/Sept. 2017 | Methanol extract/aerial parts | α-Glucosidase inhibitory test. | Compounds 76, 77 and 78 exhibited high inhibition of α-glucosidase with E. Coli (ATCC 25922), K. IC<sub>50</sub> = 0.05, 0.17, and 0.04 μg/mL, respectively, compared to acarbose (IC<sub>50</sub> = 0.25 μg/mL) as a positive control | [145] |
| 87, 88, 89, 90, 91, 92, 23, and 93 | Scrophularia syriaca Benth./Scrophulariaceae | Aljouf region (north)/May 2016 | Ethanol extract/aerial parts | Compounds 88 showed high antiprotozoal activity with EC<sub>50</sub> ranging from 1.10 ± 0.18 μM to 8.34 ± 1.70 μM, while compounds 90, 23, and 93 exhibited mild-to-moderate activities, with EC<sub>50</sub> ranging from 5.34 ± 0.52 to >100 μM compared to pentamidine | [146] |
| 94, 95, 96, 97, 98, 99, 100, 101, and 102 | Nuxia oppositifolia (Hochst.)/Buddlejaceae | Wadi Lajab (south)/Mar. 2015 | Alcoholic extract/aerial parts | Radical scavenging activity | Compounds from 94 to 98 showed the ability to reduce the DPPH and (ABTS<sup>+</sup>) radicals with IC<sub>50</sub> = ranging from 27.3 to 68.1 μg/mL | [147] |
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101682294); Isoimperatorin: (PubChem CID: 68081); Bergapten: (PubChem CID: 2355); Isopimpi
nellin: (PubChem CID: 68079); Quercetin-3-O-α-glucuronide: (PubChem CID: 5274585); Quercetin-
3-O-α-L-rhamnoside: (PubChem CID: 5280459); 3,3′-di-O-Methyllellagic acid: (PubChem CID:
5488919); Scopolioside B: (PubChem CID: 45360375); Scopolioside D: (PubChem CID: 6918700);
Scopolioside D2: (PubChem CID: 6450157); 8-Acetyl harpagide: (PubChem CID: 9978650);
Kaempferol-3-O-rutinoside: (PubChem CID: 5318767); Hispidulin: (PubChem CID: 5281628);
Ja
ceosidin: (PubChem CID: 5379096); Verbascoside: (PubChem CID: 5281800); Isoverbascoside: (Pub-
Chem CID: 6476333); Conandroside: (PubChem CID: 11192794); β-Sitostosterol: (PubChem CID:
222284); Katononic acid: (PubChem CID: 9981416); Oleanolic acid: (PubChem CID: 10494).

**Figures:**

19. Carvacrol
20. Garcinnamine E
21. 4α-(β-Glucopyranosyl)-oxy-9α-hydroxyguai-10(14)en-12,6α-olide
22. 1,11-(1,3,7,9-Tetrahydroxydibenzo[5,6]furan-2,8-diyl)bis(ethan-1-ol)
23. Quercetin
24. Kaempferol
25. Myrcetin 3,7,30-trimethyl ether
26. 3-Methoxy- querce-tin
27. Fernuginol
28. 5,6-Dehydro sugiol
29. Forskolin
30. Sugiol
31. R
32. R1, R2, R3
33. (Apigenin)
34. galactose
35. glucose
36. di-glucose
37. acetyl glucose
38. gluco, rhamnose
39. gluc, rhamnose
40. O-Xylose, galactose
41. R (Kaempferol-3-xylre-7-galactoside)
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64 Gallic acid

65 Patuletin 7-O-β-D-glucoside

66 [(Z)-1'-(2,2'-Bithiophen]-5-yl)-8''-chloro-6'',11''-dimethyldodeca6'',10''-dien-2''-yn-9''-one], tagettannin A

67 [3,4-Bis-(galloyl-3,5-dimethyl ether)-β-D-glucopyranose], and tagettannin B

68 R = rhamnose (Rhamnazin tri-glycoside)

69 R1 = R2 = H (ISorhamnetin 3-O-(6''-O-α-rhamnosyl)-β-galactoside)

70 R1 = H, R2 = rhamnose (ISorhamnetin 3-O-(2''-O-α-rhamnosiyl)-β-galactoside)

71 1β-Hydroxy-8-oxo-cyperone

72 7α-Hydroxystigmasterol
7. Clinical Trials of Nigella sativa (Black Cumin Seeds), a Plant Introduced into SA, with Other Plants Recommended for Clinical Trials

The Prophet Muhammad (PBUH) said that ‘In the black cumin, there is a cure for every disease except death’ [148]. In SA, N. sativa L. is commonly cultivated in the central and western regions [149]. In 2030, SA is expected to be the 17th and 12th among the top 50 countries/territories for diabetes and obesity prevalence, respectively [150]; about 60% of diabetes cases, especially type 2 diabetes, can be directly attributed to obesity [151]. N. sativa supplementation was evaluated for its potent activity in various studies on diabetic Saudis. When 92 patients with type 2 diabetes took different doses of N. sativa (1, 2, and 3 g) daily for 3 months, their blood glucose significantly decreased at a dose of 2 g/day [152]. Furthermore, healthy volunteers in another survey exhibited a decrease in blood glucose level after 2 weeks of taking 2 g/day of N. sativa, indicating that this is an optimal dose [153]. Therefore, a study evaluated the effect of 2 g/day of N. sativa orally for 1 year in 57 type 2 diabetic patients in addition to oral hypoglycaemic agents. In comparison with the control group (57 patients with the same regimen of placebo), there was a significant decrease in the total cholesterol (TC), blood pressure, and heart rate of the patients who took N. sativa. The decrease in TC, low-density lipoprotein (LDL-C), TC/high-density lipoprotein (HDL-C) and LDL-C/HDL-C ratios, diastolic blood pressure, systolic blood pressure, and mean arterial pressure compared with controls reflect the protective role of N. sativa against cardiovascular diseases associated with diabetics, without any reported side effects [154]. This cardiovascular activity confirmed the data of Bamosa and colleagues, where 30 diabetic patients received the same dose of N. sativa (2 g/day) for 1 year, showing a protective effect against cardiac diastolic by enhancing the systolic function of patients [155]. Moreover, glycaemic control improved as fasting blood glucose and HbA1c were reduced in all readings over the year, which may be related to enhanced insulin secretion.
by *N. sativa* [156]. Patients with diabetic nephropathy are at an increased risk of chronic kidney diseases (CKD). In a study, 32 patients with CKD stages 3 and 4 due to DN received 2.5 mL of *N. sativa* oil once orally every day for 12 weeks, and antidiabetic properties were reported. The patients’ glycaemic control and renal function improved due to a reduction in blood glucose, blood urea, serum creatinine, and 24 h total protein levels in the urine in addition to an increase in haemoglobin level, glomerular filtration rate, and total urinary volume in 24 h, with few side effects compared with patients who received only conservative drugs [157]. *N. sativa* was reported to have anti-asthmatic effects in a clinical study on 76 asthma patients; 24 patients received a placebo only (control group), and the rest were divided into two groups and received different doses of *N. sativa* (1 and 2 g/day) for 3 months. An increase in both forced expiratory flow (25–75%) and forced expiratory volume at 1 s was observed in the group treated with 2 g per day of *N. sativa* in addition to an improvement in peak expiratory flow and serum IFN-γ in both groups. Serum IgE and FeNO decreased in both groups compared with the control group, reflecting the ability of *N. sativa* to control asthma by reducing bronchitis [158].

In SA, studies have focused on the effects of *N. sativa* in diabetic patients; however, other clinical studies on Saudi Arabian plants have reported potent diabetic effects in vivo, including *Ricinus communis* L. [159], *Caralluma sinaica* (Decne.) A. Berger [160], *Murraya koenigii* L., *Olea europaea* L. [161], *Rosmarinus officinalis* L. [162], *Hammada saticornica*, *Teucrium Oliverianum,* and *Allium cepa* L. [163], in addition to the reported antidiabetic effects of various active compounds [164]. Furthermore, *N. sativa* has been reported to have various antimicrobial, anti-inflammatory, antitumour, and antioxidant clinical activities [165], while clinical studies in SA focus only on diabetes. Many other plants have been recommended in the Holy Qur’ān and Ahadith [50], including the date. Prophet Muhammad (PBUH) stated: ‘Whoever ate seven Ajwa dates in the morning ‘from the area of Aaliyah’ will not be harmed by poison or magic the rest of that day’ [166]. Even though SA is considered the third-largest producer of dates after Egypt and Iran [167], there are no clinical studies to confirm its activities compared with those of synthetic drugs. In addition, most of the studies focused on compounds isolated from the aerial parts mainly leaves of plants from the western and southwestern regions as in Figures 6 and 7 which encourages the study of different plant parts throughout the kingdom.

![Figure 6. Plant parts that are commonly used for the isolation of bioactive compounds.](image-url)
8. Conclusions and Future Directions

SA features unique characteristics, including climate, location, geographical nature, and religion. These environmental and social conditions have resulted in SA becoming home to plant species with high biodiversity. The predominantly desert nature and continuous movement of nomads have enriched the traditional uses of plants and ethnopharmacology as part of the cultural heritage. About 102 isolated active compounds have been reported as leading compounds for the treatment of serious diseases, including cancer, inflammation, diabetes, and microbial infections. Most of these compounds are isolated from the aerial parts (mainly leaves) of plants from the western and southwestern regions, especially in the spring and winter. Their modes of action, mechanisms, and synthesis strategies require further investigation to obtain an in-depth understanding of these precious resources and their bioactive compounds. The clinical trials for *N. sativa* against diabetes are ongoing and show great promise. Other plant families, including Asteraceae and Apocynaceae, are being developed in clinical trials against cancer, paving the way for new potential therapeutic entities. Conservation and management of these valuable species is highly recommended and requires the cessation of anthropogenic activities that harm the distinctive and unique characteristics of SA that allow these species to flourish.

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References


