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Review Article

RECENT ADVANCES IN APPLICATIONS OF ACTIVE CONSTITUENTS OF SELECTED MEDICINAL PLANTS OF DHOFAR, SULTANATE OF OMAN

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ABSTRACT

The Dhofar region of Oman is extremely opulent in plant biodiversity in comparison to other parts of the country. Most of the cultivated, medicinal and wild plants of the region are available in the mountainous side and hilly areas of Dhofar. The plants produce products from primary metabolism and others from secondary metabolism. On the basis of active constituents plants can be categorized into two groups:

1. Medicinal plants and
2. Aromatic plants.

Over 250 complex chemicals have been recognized and extracted from herbal sources. In this review article, we discuss a selection of medicinal plants of the Dhofar region of Oman which are rich in active constituents and through recent reports discuss the application of the most active constituents. Among the medicinal plants of the Dhofar region, frankincense is also a well-known indicator of the region and has a unique position through its medicinal properties of its oil and gum resin.

Keywords: Dhofar, Secondary metabolites, Frankincense, Active constituents.

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INTRODUCTION

The Dhofar region of Oman is significant and extremely rich in plant biodiversity in comparison of other parts of the country. Most of the cultivated, medicinal, and wild plant species of the region are found in elevated areas of Dhofar. Medicinal vegetations are the most selected sourced drugs that are able to protect the life of the majority of the world's population. Plants and herbs are the first foundation of treatments available to primitive human being. There are numerous textual references available in literature that describe the use of herbal medicine worldwide for defensive and healing purposes [1,2]. The bioproducts of medicinal plants are very beneficial in a number of ways. Some sections, for example, leaves, root, stem, bark, and sometimes even whole plants are used to create chemical brews that are useful to treat even very common problems such as throat infections and irritation. The products of the plant can be grouped into two categories:

1. Products produced from primary metabolism
2. Products produced from secondary metabolism.

The products of primary metabolism have a direct role in the growth and development of the plants. The majority of the active constituents are the products of secondary metabolism of the plants. Typically in adverse condition, plants shift their metabolism from primary to secondary to protect itself from adverse conditions. Some of the secondary metabolites synthesize in response to injury to plants. Plants accumulate several secondary metabolites to protect themselves against insects, fungi, and herbivorous animals. On the basis of active constituents, plants can be categorized into two main groups: First, medicinal plants and second, essential oils bearing medicinal plants also known as aromatic plants.

The use of oil extracted plants such as castor, garlic, mint, coriander, and opium has been reported from the era of the early civilization of Egypt and was popular among trade goods during the Roman Empire [3]. For example, spices are aromatic or pungent vegetable substances applied in minute amounts to augment, modify or mask the aroma of food [4]. Spices have been used since ancient times for the protection of food products as they possess antiseptic and disinfectant properties [1,2]. They enhance the shelf life of foods by avoiding rancidity and oxidation of lipids [5] or by bacteriostatic or bactericidal activity and antifungal activity. Compounds obtained from plants known as phytochemicals have attracted much attention as natural alternatives to synthetic drugs. These natural products are used as raw materials to synthesize new antimicrobial and antifungal drugs which are relatively safe to humans and help to supply synthetic chemicals. In excess of 250 complex chemical extracts are identified from herbal sources. Ethnobotany is the stream of science that deals with the study of the old-fashioned application of plants for humans and is a very useful way to discover the herbal medicine [6]. Herbal drugs for various societies of poorer nations are found to be more economical in comparison to modern pharmaceuticals. It is well documented that more than 80% of the population of the third world rely on herbal medicine for their healthcare needs. Societies of developed countries also use herbal components for fragrances and other cosmetic purposes. Various aspects in the study of active constituents have changed and upgraded due to an advance in technology and methodology. Scientists are working hard to ensure quality control, scientific evidence for the efficacy and for the prevention of potential adverse effects of herbal remedies. Active constituents such as alkaloids, flavonoids, flavones, terpenes, and polyterpenes which are present in different organs of the plants have various effects on biological systems. Attention has been geared toward developing new antibiotics which reduce the increasing resistance

among microorganisms [7]. In this review article, selected medicinal plants of the Dhofar region of Oman which are a rich source of active constituents, advancement of extraction, and isolation technology are addressed together with recent reports on the application of the most active constituent. Among them, frankincense is a well-known indicator of the region and has a unique position due to the medicinal properties of its oil and gum resin.

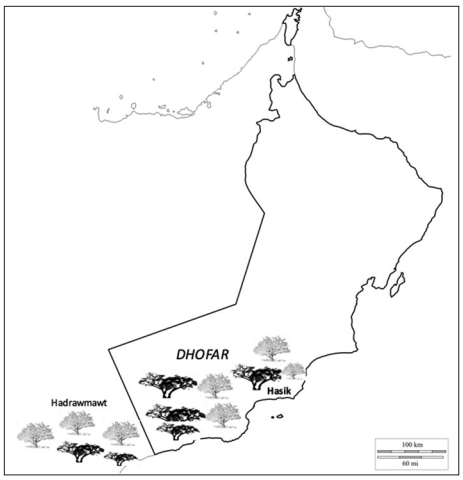
FRANKINCENSE (*BOSWELLIA* SPECIES)

Several of the approximately 25 species of *Boswellia*, including *Boswellia sacra* (from the southern Arabian Peninsula), *Betula papyrifera* (from the tropical Northeast Africa), *Boswellia frereana* (from Somalia), B. soqatra (from the tropical island of Socatra in the Indian Ocean), and *Boswellia serrata* (from India) produce a unique oleo-gum-resin from cutting the small ducts in the bark of trees from which the gum resin's frankincense are collected (Photograph 1). Characteristics of the species allow them to be burned as a sweet fumigate as well as to be distilled as a fragrant perfume or often dissolved in water to be consumed for medicinal purposes as a pulmonary antihistamine. This is common traditional practice today among locals living in these regions.

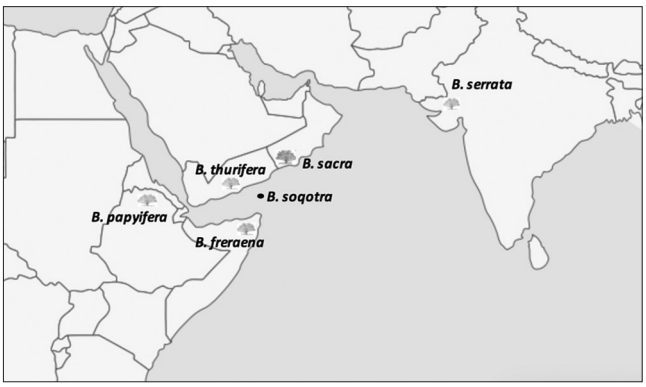
While the etymology of the Anglo-Saxon word frankincense belongs to the French language which means "pure incense," frankincense as a globalized trade commodity in world history is known by various different names in different cultures. Other names for frankincense are *Olibanum*, *Salai guggal*, *Luban*, or *Kundur*. Linguistically, *Olibanum* may first appear in ancient cuneiform tablets from third Millennium BC Mesopotamia where it was used as medicinal oil [8]. *Kundur*, the classical Arabic word for frankincense, can be traced back to the ancient Sanskrit language as the oleo-gum from the B. serrata tree [9,10]. As the most renowned plant of Dhofar, the *B. sacra* frankincense tree is known today as *Shajarat al-luban* in Dhofari Arabic and as *Megerot.* In the modern South Arabian Jibbali language of the mountains of Dhofar [11]. Today, the species *B. sacra* grows from the Hadhramaut in Yemen to Hasik in Dhofar (Map 1; Map 2; Table 1).

In general, in almost all of the cultures where frankincense was traded, it was used for fragrance and fumigating objects used in religious ceremonies. In traditional medicine, frankincense has a unique place among the remedies for treating various disorders [12]. Frankincense was commonly used to treat microbial infections as early as the 11th century. As per the report published by Michie and Cooper [13], the Persian physician and philosopher Avicenna studied the effect of frankincense on urinary disorders such as inflammation and common infections and found that frankincense had an effective role to treat this type of an infection.

Gum resins of *Boswellia* sp. have wealth of healing properties and used to treat rheumatoid arthritis and other inflammatory diseases [14]. There are numerous reports which explain the importance of frankincense in treating various infectious caused by different pathogens and



Map 1: Distribution of *Boswellia sacra* trees from the Hadhramaut (Yemen) to Dhofar (Oman)



Map 2: Agricultural distribution patterns of the *Boswellia* species

Table 1: Main species of *Boswellia* and their location of cultivation

S. No	Name of species	Location of cultivation
1	*B. serrata*	Northwest India
2	*B. frereana*	Somalia and Ethiopia
3	*B. papyrifera*	Ethiopia, Eritrea, and Sudan
4	*B. thurifera*	Yemen, and North and East Africa
5	*B. soqotra*	Island of Soqotra
6	*B. sacra*	Dhofar

B. serrate: Boswellia serrate, B. frereana: Boswellia frereana, B. papyrifera: Boswellia papyrifera, B. thurifera: Boswellia thurifera, B. soqotra: Boswellia soqotra

Table 2: Metabolites and their components of *Boswellia* sp.

S. No	Metabolites	Main components	Percentage
1	Resin	Mixture of terpene	65–80
2	Gum	Mixture of polysaccharides	6–25
3	Essential oil	Components are listed in Table 3	5–7

Photograph 1: *Boswellia sacra* cut from the bark of a Frankincense tree at the site of al-Shishr, Dhofar (Photograph by W. Zimmerle)

other medical conditions [15,16]. The composition of various parts of *Boswellia* sp. including the component of essential oil is already discussed in detail. We reviewed here the recent use of secondary metabolites extracted from various sources a variety of *Boswellia* from regions such as Oman, Yemen, and Somalia which are known as major trading centers of frankincense from as early as the first millennium BC [17].

SECONDARY METABOLITES OF *BOSWELLIA* SPECIES

There are various compounds found in *Boswellia* species, the quantity and quality of these compound changes from species to species that makes every species different from one another (Table 2). The reasons behind these differences are closely related to climate, harvesting time, and geographical conditions [18,19]. The leaves extract of *Boswellia* species contains steroids, terpenoids, fatty acids, tannins, saponins, anthocyanin, leukoanthocyanin, coumarins, emodins, alkaloids, phenols, and flavonoids. The chemical composition of frankincense essential oil can be used as a marker to recognized varieties of frankincense. The important component of Omani and Aden essential oil is α-pinene (43%) whereas; Eritrean and Turkish essential oils have a high quantity of octyl acetate (52%). The Indian oil is rich in α-thujene (61% Fig. 1a) [20-24]. The major metabolites of frankincense are highlighted as follows [25,26]:

Monoterpene is a major group (monoterpene hydrocarbons) which is found in frankincense oil up to 40%; however, there are some variations existing among species of *Boswellia* on the basis of monoterpenes concentration [27]. The main composition of essential oil was α-pinene 45.7%, α-terpinene 11.5%, and trans-sabinene hydrate. The components of essential oils show variation from species to species, components listed in Table 3 are found in most of the oils extracted from various species of *Boswellia* [18].

Components of resin

Like essential oil, the resinous part of frankincense has terpenes such as α-thujone (monoterpenes), diterpenes, α-and β-amyrins (triterpenes), boswellic acids (BAs) (pentacyclic triterpenic acids), tirucall-8, and 24-dien-21-oic acids (tetracyclic triterpenic acids). Among these, the BA is the most important active component of *Boswellia* species [18] Table 4.

Use of frankincense oil

Frankincense essential oil is used to treat several inflammatory diseases such as arthritis, bronchial asthma, chronic colitis, and cancer and also used in dermocosmetics, inhalation, and smoking [28-30]. Essential oil also showed antibacterial, antifungal, and immunostimulating activity [31]. The essential oil extracted from *B. sacra* is generally rich in alpha-pinene. The challenge of microbial chemo control lies in the development of new microbial strains with high resistance to the classical and advance antibiotics [32].

Use of frankincense oil against pathogens

Researchers concerning the antimicrobial activity of phytoproducts such as phytochemicals, vitamins, and hormones have been studied extensively yet there is little emphasis on the evaluation of the antipathogenic effect of essential oils and extracts [33]. The antipathogenic activities of the essential oils were independently evaluated against fungi, Gram-positive, and Gram-negative bacteria strains. Resins of frankincense destroy the cell wall of the pathogen and prevent protein synthesis in *Streptococcus salivarius*, *Staphylococcus aureus*, and *Bacillus megaterium* [34]. Volatile oils make sensitization of microbial cell contents and have anti-bacterial effects on *Staphylococcus epidermidis*, *S. aureus*, *Staphylococcus hominis*, *Bacillus cereus*, *Proteus vulgaris*, *Escherichia coli*, and *Candida albican* [35]. Application of frankincense products such as gum, oil, and extracts can significantly decrease in inflammatory indices compared to drug therapy. It is a secure and economical form of herbal drug and may be plausibly used to treat inflammation based ailment of gingival as an accessory to the therapy. The essential oil and methanol extract of *Boswellia* displayed activity against bacterial spp. than against yeast [36]. Kavanaugh and Ribbeck tested the antimicrobial activity of some essential oils against *Pseudomonas aeruginosa*, *Pseudomonas putida*, and *S. aureus* [34,37]. However, results obtained by Rashan *et al.* (2017; unpublished) indicated that no effect of frankincense oil was found on various species of genus *Staphylococcus*. They are known to taint important tracts such as pulmonary, trachea and urinary tracts, lesions, and scorches. The combined dose of myrrh and frankincense essential oils showed synergistic effects on *Cryptococcus neoformans* and *P. aeruginosa* [4].

Table 3: Major component of frankincense essential oil

S. No	Major component	Description
1	Monoterpene	Monoterpenes are the major parts of essential oil. To date, there are at least 30 types of monoterpenes are reported in frankincense oil. Among these, alpha-thujene, E-beta-ocimene (Fig. 1b), camphene, sabinene (Fig. 1c), myrcene, Alpha-pinene, limonene, alpha-thujene, E-beta ocimene, and camphene are important and share major part of secondary metabolites
2	Diterpene	Cembrene (Fig. 1d), isocembrene, verticiol, duva-4,8,13-trien-1,3α-diol, thunbergol, duva-3,9,13-trien-1,5α-diol, duva-3,9,13-trien-1α-ol-5,8-oxide-1-acetate, duva-3,9,13-trien-1,5α-diol-1-acetate
3	Sesquiterpene	Sesquiterpenes are other major components of frankincense oil. The main sesquiterens are alpha-cubebene (Fig. 1e), alpha-copaene, betabourbenene, beta-elemene (Fig. 1f), E-caryophyllene, alpha-humulene, allo-aromandendrene (Fig. 1g), etc.

Table 4: Components of resin

S. No	Type	Role
1	β-BA	It can reduce the biosynthesis of DNA, RNA, and protein leukemia cells in human [27]
2	ABA	It also can inhibit the transcription and translation in HL-60 cells [27]
3	11-KBA (Fig. 1h)	ABA and KBA have similar effects to each other
4	3-O-AKBA	The anticancer activity of AKBA is linked with its inhibitory nature to lipoxygenases leading to reduction of cell proliferation as well as apoptosis induction in cells of tumors It has shown a specific inhibitory role in prostate cancer by destroying factor related to receptor 2-mediated angiogenesis [9]

BA: Boswellic acid, ABA: Acetyl-β-boswellic acid, KBA: Keto-β-boswellic acid, AKBA: Acetyl-11-keto-beta-boswellic acid, DNA: Deoxyribonucleic acid, RNA: Ribonucleic acid, HL: Human leukemia

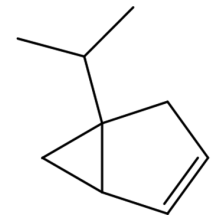
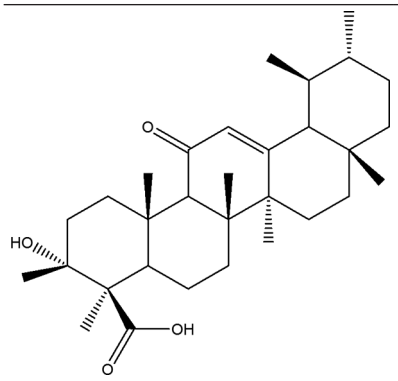
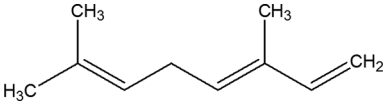
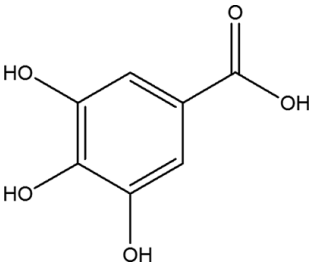
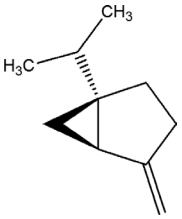
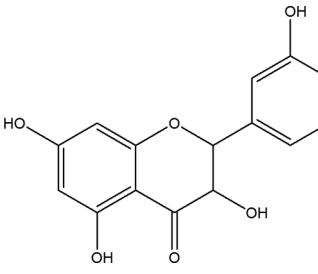
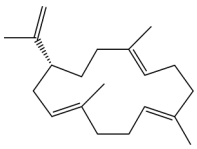
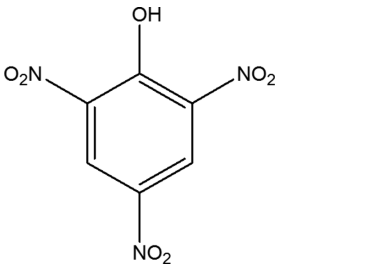
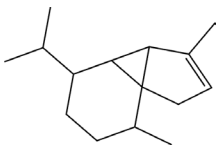
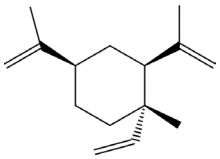
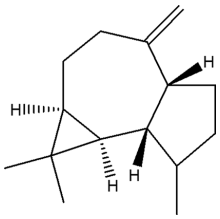
Chemical compound	Common name	Chemical compound	Common name
	α-Thujene (a)		11-keto-β-BA (h)
	E-beta Ocimene (b)		Gallic acid (i)
	Sabinene (c)		Quercetin (j)
	Cembrene (d)		Picric acid (k)
	α-cubebene (e)		
	β-elemene (f)		
	allo-aromandendrene (g)		

Fig. 1: (a-k) Chemical structures

Use of frankincense oil against cancer

Resins of *Boswellia* species have triterpenoids which are responsible for antitumor properties of resin [38]. Resin of *Boswellia* has four important types of triterpenic acid:

The BA has effect on apoptosis myeloid leukemia cell lines of human beings. *B. serrata* has pentacyclic triterpenoids which have the ability to reduce the growth and development of cancer in prostate cell [39]. Akt, which is a type of protein kinase, has various roles in cellular functionality such as cell transport, protein synthesis, cell proliferation, and apoptosis. It is also linked with several types of cancer as it can aide to reduce or even stop apoptosis and further, promote the survival of cells. Another secondary metabolite known as tirucallic acid found in gum resin of *Boswellia* carteri plays an effective role as Akt inhibitors [39]. The finding of the study indicated that application of 3600 mg/day of *Boswellia* decoction with a concentration of 60% BA decreased the fluid around the tumor in 8 out of 12 tested patients and it was also noted that damage in brain cell declined by the treatment of the extract [40]. Syrovets *et al.* (2000) reported that acetyl-BA (ABA) inhibits Topoisomerases I and IIα through competition with deoxyribonucleic acid (DNA) for binding to the enzyme [38,131]. In another study, Tatiana *et al.* detected that acetyl-α-BA (AαBA) and acetyl-11-keto-β-BA (AKβBA) slow down the activities of human recombinant glutathione S-transferase-IκB kinase (IKK)α and His-IKKβ. The lipopolysaccharide (LPS)-triggered induction of tumor necrosis factor-α in monocytes is reliant on IKK activity. These findings provided molecular basis properties ascribed to AαBA- and AKβBA-containing drugs for the anti-inflammatory and suggested that ABAs can be used as a template to develop new therapeutic drugs [38]. Berthold *et al.* identified a novel pentacyclic triterpene, lupeolic acid, from frankincense gum resins which are used to inhibit cytosolic phospholipase A2α responsible for inflammation [41,132]. Hoernlein *et al.* (1999) reported antiproliferative property of AKβBA and noted that A keto-β-BA (KBA)

inhibited 5-lipooxygenase. Further, they tested acetyl-11-keto-beta-BA on growth performance of leukemic cell growth; the finding obtained from this experiment suggested that apoptosis induced in human leukemia-60 and CCRF-CEM was due to inhibition of Topoisomerase I in these cells [38]. Clarisse Cuaz-Pérolin *et al.* (2008) studied the effect of AKβBA on the growth of atherosclerotic lesions in apolipoprotein of mice. They observed that AKβBA strongly reduced the IKK activity immunoprecipitated from LPS-stimulated mouse macrophages and mononuclear cells leading to reduced phosphorylation of IκBα and inhibition of p65/NF-κB activation [44]. Vanessa *et al.* (2004) studied the effects of connected food consumption on the bioavailability of different BAs. Data exposed comprehensive kinetics of BAs after the oral supply of extract and established a relationship between food intake and pharmacokinetic of BAs [45]. Syrovets *et al.* (2005b) studied the role of ABAs on activity of IKK and observed that ABAs promoted apoptosis in an androgen-independent PC-3 prostate cancer cell by inhibiting IKK in both *in vitro* and *in vivo* condition. On the basis of their findings, they concluded that AKβBA and associated molecules acting on IKK might offer a novel method for the treatment of chemoresistant human tumors such as androgen-independent human prostate cancers [42,43]. Berthold *et al.* (2006) observed that extract of *B. sacra* inhibited the growth of prostate cancer cells of chemotherapy-resistant human PC-3 *in vitro* and provoked apoptosis as shown by activation of caspase 3 and the induction of DNA fragmentation [45,132].

Emblica officinalis

It is an elegant decorative tree and attains a height of 18 m and, in rare cases, up to 30 m. The emblic is of countless significance in Asiatic medicine not only as an antiscorbutic but also in the dealing of diverse sicknesses particularly those related with gastric organs [43]. For such use, the fruit juice is extracted in the form of a sherbet or is fermented. In its latter state, it is used for jaundice, coughs, dyspepsia, etc. The dried chips of the epithelium are mixed with honey and grape juice for treating various minor physiological disorders. Extract obtained from emblic with *Terminalia chebula* and *Terminalia bellirica* locally known as Triphala is given for prolonged dysentery, hemorrhoids, biliousness, enlarged liver, and other disorders. Dried powder fruit is an active remedy as it stimulates the respiratory glands. The liquor, that releases from persistent fruit, has operated as an eyewash for swollen eyes [46-48].

Essential oils of *Emblica* contain tannins, ellagitannins (corilagin, geraniin, and chebulagic acid), alkaloids, phenolic compounds, amino acids, and carbohydrates. Juice of *Emblica* fruits contains the highest Vitamin C content. It is found that when the fruit is mixed with other fruits increased their dietetic excellence in terms of vitamin content. Essential oil of *Emblica* has various components including 3,6-di-O-galloyl-dglucose, gallic acid (Fig. 1i), chebulinic acid, 1-O-galloyl-beta-D-glucose, ellagic acid, quercetin (Fig. 1j), chebulagic acid, corilagin, 1,6-di-O-galloyl beta D glucose, 3 ethylgallic acid (3 ethoxy 4,5 dihydroxy benzoic acid), and isostrictiniin [49]. Habib-ur-Rehman *et al.* reported that *Phyllanthus emblica* contains flavonoids, kaempferol-3-O-alpha L-(6" methyl) rhamnopyranoside, and kaempferol-3-O-alpha-L (6" ethyl) rhamnopyranoside [48]. Another acylated apigenin glucoside (apigenin-7-O-(6" butyryl beta gluco-pyranoside) was extracted from the leaves of *P. emblica* together with the known compounds such as methyl gallate, gallic acid, 1,2,3,4,6-penta-O-galloylglucose, and luteolin-4'-oneohesperiodoside [45]. A concoction made by dehydrated fruit in water for at least 12 h has also worked as an eyewash. Liquor prepared from the inflamed fruits is recommended as a treatment for gastritis, anemia, jaundice, some cardiac problems, nasal congestion, and urine retention. The flowers and roots are also used in a number of ways. A gel made from the overcooked seeds and oil is used to skin infirmities. The various preparations of seed are prescribed in treating asthma, bronchitis, diabetes, and fevers. Seeds have enzymes such as lipolytic and proteolytic as well as phosphatides with a minor quantity of essential oil. Nosál'ová *et al.* considered the medicinal importance and observed antitussive property of *E. officinalis* gaertn. In conscious cats by stimulation of the tracheobronchial mucous areas of windpipe [46]. They noted that a dose at 50 mg/kg body weight. Applied orally, the cough tyrannical outcome of *E. officinalis* was not clear. A fundamental dose (200 mg/kg body weight) of this component applied orally was found extra effective, mainly in waning cough exertions (NE), incidence of cough (NE/min[−1]), and the number of cough rounds in inspirium (IA+) and expirium (IA−) was highly noticeable. These outcomes showed that the cough exploitive activity of *E. officinalis* is dose-dependent. It is well reported and easy to demonstrate that antitussive activity of *E. officinalis* is less effective in comparison to classical narcotic antitussive drug codeine, but more effective than the non-narcotic antitussive agent dropropizine [48]. It was proposed that the antitussive activity of the dehydrated extract of *E. officinalis* was due not only to antispasmolytic, antiphlogistic, and antioxidant properties but also to its effect on mucus secretion in the airways. Phytochemicals are currently believed as one of the most significant approaches in the control of cancer. Essential oil is treasured for its distinctive tannins and flavonoids which showed very influential antioxidant properties. The inhibition of tumor occurrences by fruit extract *Emblica* estimated on the two-stage method of skin carcinogenesis in Swiss Albino mice [51].

Aloe vera

A. vera is a herbal member of the lily family. It has a rich source of juice and can be comparable to a cactus [50]. It has fleshy, gray-green leaves in an attractive rosette display. There are over 200 species of *A. vera. A. vera* comprises up to 75 nutrients and 200 active compounds including vitamins, enzymes, minerals, sugar, glyconutrients, lignin, anthraquinones, saponins, salicylic acid, and amino acids [51]. The utmost advantageous variety of *A. vera* is *A. vera* barbadensis [52]. Specifically, *A. vera*, both taken orally and through relevant dressings is actual treatment in cases of frostbite, different types of sores, any kind of skin wound, as well as eruptions and scorches, epidemics, urticaria, hypersensitive reaction, scratches, herpes lacerations, pimples, insect bites, prickles, scalp irritation, psoriasis, and sunburn pain [53,54]. It eases dark facial acne and decreases the strength of coloration. It is applied as a conditioner and supportive in eliminating departed cells. It is also cooperative in permeation of vigorous substances [55-57]. *A. vera* holds two different classes of Aloins:

1. Nataloins, which produce oxalic acids and picric (Fig. 1k) with nitric acid, and does not provide a red coloration with nitric acid and
2. Barbaloins, which produced chrysammic acid ($C_7H_2N_2O_6$), aloetic acid ($C_7H_2N_3O_5$), and picric and nitric acid with oxalic acids.

This second cluster may be separated into a-barbaloins, b-barbaloins obtained from Barbados aloes as well as socotrine and Zanzibar aloes. Reddening occurs by nitric acid only when tepid in the cold. Nataloin creates sunny yellow scales. Barbaloin creates buttery prismatic crystals. The plant offers six antiseptic means, namely, salicylic acid, lupeol, nitrogen, urea, phenols cinnamonic acid, and sulfur. All materials were identified as antiseptics as they destroy or regulate fungus, microbes, mold, and germs revealing that the plant is capable of removing many inner and exterior infections of the body. Lupeol and salicylic acid are two very active painkillers. It includes three anti-inflammatory fatty acids, namely, cholesterol, campesterol, and β-sitosterol. These are used in the treatment of injuries, predicaments, scratches, allergic scuff, retort, arthritis, rheumatic fever, ulceras, and acid indigestion well as a variety of inflammatory problems of the digestive tract and internal organs such as the stomach, colon, small intestine, liver, pancreas, and kidney. β-sitosterol is another dominant anti-cholesterol which aides to lower dangerous cholesterol intensities extremely beneficial for heart patients. There are at least 23 polypeptides present in aloe juice which can aid the immune system of the body to protect it from various ailments and disarrays. The polypeptides, aloe-emodin and aloe lectins are now also applied to cure cancer. Stanle *et al.* examined *A. vera* gel for its microbial activity [58]. He used ethanol, methanol and an aqueous extract solvent for extraction. He reported that aqueous extract had the maximum production (19.0 g) after extraction in comparison to ethanol (18.40 g) and methanol (18.0 g). However, ethanol is still considered as the best solvent for extraction. Agar well diffusion method was used to check the vulnerability of *E. coli*, *S. aureus*, and *C. albicans* to

the crude extracts of *A. vera* gel. They used both negative and positive controls by taking gentamycin as the positive control while dimethyl sulfoxide being the negative control [56]. The ethanol extract proved better in comparison to aqueous extract as it showed to decrease the growth of *C. albicans*, *S. aureus*, and *E. coli* with zones of inhibition of 4, 5, and 6 mm while the water extract had zones of inhibition of 3, 4, and 6 mm, respectively. The lowest response registered by methanol extract as it decreased the growth of *E. coli* (3 mm) only. Another report by Ferro *et al.* suggested that *A. vera* leaf gel is capable to inhibit the growth of two Gram-positive bacteria *Shigella flexneri* and *Streptococcus pyogenes* [59]. Particular secondary metabolites of *A. vera* such as anthraquinones [58,59] and dihydroxyanthraquinones [60] as well as saponins [61,62] have antimicrobial activity. Further, Shamim *et al.* reported the highest inhibition by ethanol extracted from *A. vera* baradenisis against *Candida* species [63]. Polysaccharide component from whole plant material has antimicrobial activity as it encourage phagocytic leukocytes [64]. Bajwa and Shafique examined the antipathogenic activity of *A. vera* extract against *Alternaria alternata*, *Alternaria citri*, and *Alternaria tenuissima* and found that *A. vera* extract made a toxic effect on mycelial growth and proliferation of these member of alternaria [65]. Further, he noted that a dose of *A. vera* gel at 0.25% was more pronounced against *Aspergillus flavus* compare to *Aspergillus niger*. Another report published explained the antifungal effect of *A. vera* on various varieties of *Aspergillus* including *A. flavus*, *Aspergillus glaucus*, and on other fungal agents such as *C. albicans*, *Candida tropicalis*, *Trichophyton mentagrophytes*, and Trichophyton rubrum [66-68]. The dose of *A. vera* gel at 0.35% was active at the maximum against all tried fungi. At this dose, mycelial growth decreased at 24.29% in *A. niger*, 9.26% in *A. flavus*, and only 6.24% in *Penicillium digitatum*. Cock also noticed antifungal property of *A. vera* gel by testing it on *A. niger* [67]. In view of Arunkumar and Muthuselvam, acetone extract of *A. vera* showed the highest antifungal activity against *A. niger* and *A. flavus* [69]. Acemannan, from *A. vera* gel, has antiviral and antitumoral properties. Lee *et al.* extracted and purified acemannan from *A. vera* and observed that acemannan has positive effect phenotypic and functional maturation of immature dendritic cells [68].

Cuminum cyminum

C. cyminum, a member of family Apiaceae, has been commonly cultivated in Asia, Africa, and Europe from very early periods of civilization and considered as one of the earliest cultivated herbs. *Cumin* seeds are used in traditional remedies and considered eupeptic, acerbic, antispasmodic, and carminative and have been applied to cure mild digestive ailments, diarrhea, indigestion, gassiness, morning sickness, bellyache, dyspeptic headache, and inflating and are said to encourage the assimilation of other herbs and to improve liver function. It is used to treat bronchopulmonary disorder as well as a painkiller. Seeds of cuminum are used to treat lambago and rheumatism. Essential oil of *C. cyminum* L is an antibacterial, anti-inflammatory, a palliative hemolytic, or antienzymatic action [68]. Seeds of *C. cyminum* are carminative, sweet-smelling, stomachic, intoxicating, caustic, and freshening in effect [69]. Cumin seed oil is used as multifunctional glowing dyes or in topical coagulating ointment [70]. In the treatment of scabies, a mixture of castor oil and alcohol is generally applied, and it was noted by Joshi and his team that it significantly controlled scabies [71]. Various scientists studied the composition of cumin seeds and discovered that they possessed various classes of secondary metabolites such as hydrocarbons, monoterpene, oxygenated monoterpenes, saturated and unsaturated fatty acids, oxygenated sesquiterpenes, aldehydes, esters, and ketones [72-74]. Other reports mentioned some primary metabolites such as fatty acids, triacylglycerols, polysaccharides, and lignin in cumin seeds [75,76]. Yetim and co-workers studied the composition of seed and reported a nonspecific lipid transfer protein [77]. Reports of El-Sawi and Mohamed, Al-Bataina *et al.*, Maiga *et al.*, and Milan *et al.* mentioned that cumin seeds have nutrients such as amino acids, vitamins, protein, minerals, carbohydrates (sugars, starch), tannins, dietary fiber components, and phytic acid [78-83]. Oils and extract of cumin seeds have antimicrobial activity against useful and pathogenic Gram-positive and Gram-negative bacterial strains [73,82-85]. Dorman and Deans studied the antimicrobial activity of oil and extract of cumin seeds and found that both oil and extract of cumin seeds inhibited the growth of *Klebsiella pneumonia* [86]. They suggested that limonene, eugenol, pinene, and some other minor constituents contribute to the antimicrobial activity of cumin oil. Further, Burt observed that carvacrol chemically known as 5-isopropyl-2-methylphenol devises antimicrobial activity against both Gram-positive and negative bacteria [87]. Various reports clearly indicate that cumin oil has antifungal property against food, soil, human, and animal pathogens such as dermatophytes *Vibrio spp*., aflatoxins, yeasts, and mycotoxin producers [73,83,86,87]. It is also observed that sufficient supplementation of cumin in diet decreases the chances of colon cancer in rats induced by colon-specific carcinogen. In those animals that received a sufficient quantity of cumin in their food were found healthy and showed no sign of colon tumors [88,89]. Cumin supplementation in diet can decrease the chances of benzopyrene-induced forestomach tumorigenesis, 3-methylcholanthrene induced uterine cervix tumorigenesis and 3-methyl-4-dimethyaminoazobenzene induced hepatomas in mice. The capacity of cumin to inhibit various cancer cells is due to its ability to modulate carcinogen metabolism through carcinogen/xenobiotic metabolizing Phase I and Phase II enzymes [90,91].

Cumin oil has influences on compound-metabolizing enzymes and acid-sol compound in plant seeds and regulate the sulfhydryls in liver [68]. Hussain *et al.* stated the key constituents are cuminal and safranal 32.26% and 24.46%, respectively [72]. Soniya *et al.* studied the antibacterial property of cuminum extract against *E. coli* and found that it could control the infection cause by *E. coli* [92]. Another study indicated that essential oil of C. cyminum is useful to inhibit the infection caused by *E. coli P. aeruginosa* and *Salmonella sp.* Experiment conducted by Keskin and Toroglu was sufficient to show that methanol extracts of cuminum have no inhibitory effect against pathogen like *Rosenbergia rubra* [91]. Ouattara *et al.* suggested that antibacterial activity of cuminum due to carvone and carvacrol was found in its volatile oil [94]. Shetty *et al.* studied the effect of essential oil of cumin on ungi, yeast, and bacteria [95]. According to their findings cumin, essential oil had high effects on fungi and yeast than that of bacteria.

Rhazya stricta

R. stricta decne (*R. stricta*) is the member of family *Apocynaceae*, locally known as harmal, which is commonly found in Asia. It was the main source of raw material used to treat several types of physiological disorder including sore throat, rheumatic pain, syphilis, helminthiasis, diabetes, fever, inflammatory conditions, and other diseases. *R. stricta* has more than 100 indole alkaloids including akuammidine, rhazinilam, and tetrahydrosecamine [95,96]. Baeshen *et al.* studied the chemical composition of leaves of *R. stricta* and found that leaves have several types of primary and secondary metabolites including flavonoids, glycosides, triterpenes, tannins, volatile bases, and probably other substances [97]. Due to its medicinal properties, scientists explored it in all aspects of studies including phytochemistry, antimicrobial activity, central nervous system (CNS) depression and also in general pharmacology as well as the toxicity of the plant [98-104]. There are several reports which explained the biological and physiological effect of the extract obtained from leaves of *R. stricta*. Extract obtained from leaves of *R. stricta* caused drowsiness, insensibility, reduced motor movement and various other effects on brain activity. Ahmad *et al*. studied the effect of leaves, flower and fruit on joint infection and cancer, and found some positive response [99]. Baeshin *et al.* claimed to study the first time genotoxic effect of the *R. stricta* leaf aqueous extract as an antifungal agent against *Saccharomyces cerevicae* auxotrophic mutant [105]. Furthermore, in another study, Baeshin *et al.* reported the biochemical and molecular evaluation of genetic effects of *R. stricta* (decne) leaves extract on *Aspergillus terreu* [106]. However, there are still very few reports that deal with the antimicrobial effects of the leaf extract of *R. stricta*. Ansah *et al.* and Baeshin *et al.* observed in their study with *Cryptolepis sangvinolehta* and A. terreus that leaf extracts of *R. stricta* produced free radicals which can interact with plasmid DNA to identify the deletion [106,107]. The ability of *R. stricta* leave extract

to apply a stress on the bacteria was confirmed by results of sodium dodecyl sulfate-polyacrylamide gel electrophoresis protein profile, the decrease of total protein and expression of new proteins due to the treatment. Such type of stress caused the induction and expression of proteins in treated bacteria. Similar effects were observed by Baeshin *et al.*, and Burt and Reinders in *S. cerevicae* and *E. coli* by the application of oregano and thyme essential oil, both worked as strong antimicrobial agents [106,108,109]. Burt explained the mode of action of secondary metabolites as mostly being obtained by essential oil against bacterial cell [89]. He suggested that the systematic damage in bacterial cell followed the following events:

1. Degradation of the cell wall damage, cytoplasmic membrane proteins, the binding of proteins;
2. Leakage of cell contents;
3. Coagulation of cytoplasm; and
4. Depletion of the proton motive force.

The leaves extract of *R. stricta* reduced the quantity of triglycerides, low-density lipoprotein-c, cholesterol, uric acid, and creatinin and enhanced the concentration of high-density lipoprotein-c. The leaves extract of *R. stricta* increase and decrease all the components above with any effect on the liver and kidney function. Singhal *et al.* used high doses of leaves extract to study the toxic effect on physiological parameters [110]. He found that supply of 0.25 g/kg/day leaves of *R. stricta* increased the cholesterol level in sheep within 42 days. He concluded that *R. stricta* has capacity to cure hypercholesterolemia and hypertriglyceridemia. However, he suggested the need for further investigation to confirm the results obtained by him. He also suggested further study of the possible mechanism of action of leaves extract of *R. stricta* on human cardiovascular disorders. Shahat *et al.* (2016) investigated the antitumor activity of *R. stricta* in chemically-induced hepatocellular carcinoma (HCC) in rats. They observed that findings of experiment support antitumor efficacy of *R. stricta* against HCC and work as hepatoprotective properties, antiproliferative activity, and antiangiogenic potential [100]. El-Awady *et al.* (2015) investigated the anticancer potentiality of *R. stricta* grown in Saudi Arabia. Different extracts were utilized against HCC (HepGII) and colon cancer (CaCo) cell lines. Extract showed the highest cytotoxic effect among all extracts with caco cells (IC50 25 μg/ml and 35 μg/ml) and HepG2, respectively [101].

Calotropis procera

C. procera (Ait) R.Br. (*Asclepiadaceae*) is a plant which is widely cultivated throughout the whole region of Asia and Africa and the Middle East. This plant is commonly acknowledged due to the richness of latex [110]. Latex is a mixture of various secondary metabolites, such as glycosides, tannins, and many proteins, among others [112,113]. *C. procera* is an important source for Ayurveda. *Calotropis* is represented by two species, namely, *Calotropis gigantea* (Linn.) R.Br. and *C. procera* (Ait.) R.Br [109]. It has been broadly recycled in the Sudanese, Unani, Arabic, and Indian traditional medicinal system so as to treat various diseases, namely, leprosy, ulcers, piles and diseases of the spleen, liver, and abdomen [114]. Various parts of *Calotropis* have several biological activities such as proteolytic, antimicrobial, larvicidal, nematocidal, anticancer, and anti-inflammatory [115]. The latex of *Calotropis* can be applied to heal the wound and also used as anti-diarrhea, anti-inflammatory, and anti-rheumatism agent [116]. The anti-bacterial property of *Calotropis* latex is due to the presence of active components such as calatin, mudarin, and calotropin [117,118]. Shittu *et al.* studied the effect of latex obtained from *C. procera* on total viable count and found that the ethanolic extract of both leaf and latex reduced the growth of fungi, namely, *R. stolonifera* [119]. Almost similar findings were reported by Kareem *et al.* against fungal strains [120]. Freitas et al. examined the reducing power of latex extract of *C. procera* against Fusarium solani [120].

Nerium oleander

N. oleander is a perennial shrub that belongs to *Apocynaceae* (dogbane family). All sections of the plants are toxic. However, the sections such as leaves, roots, and root bark can be applied to cure different disorders. Charka, a well-known Indian Practitioner of Ayurveda, used leaves of nerium to treat skin disease including leprosy. Various reports published on nerium suggested that it can be used in various disease such as dermatitis, carbuncles, herpes, eczema, lesions, psoriasis, verrucae, asthma, scabies, slops, ringworm, dysmenorrheal, epilepsy, malaria, abortifacients, emetics, heart tonics, and tumor [121]. Khare studied the properties of *N. oleander* and observed that it can actually cause the ulcers and induce abortion [122]. Hseini *et al.* reported that leaves of *N. oleander* contained very high amounts of polyphenol [123]. The major secondary metabolites of *N. oleander* are cinnamic acid, an antioxidant, anti-diabetic, and hepatoprotective [124]. Rashan *et al.* 2011 studied anticancer activities of extracts and isolated cardenolides. They observed that results were in agreement with the ethnomedicinal use of *Streptocaulon tomentosum* and *N. oleander*. The highly active compounds from both species were monoglycosidic cardenolides having the 3β,14β-dihydroxy-5β-card-20(22)-enolide structure with or without an acetoxy group at C-16. The findings showed that the cytotoxic effects are made by the inhibition of the plasma membrane-bound Na(+)/K(+)-ATPase [125]. Mohadjerani conducted an experiment to study the property of leaf extracts of nerium and found that extract with methanolic decoction and N-butanol extract showed more activity than that of phenolic extract. On the basis of his findings, Mohadjerani explained that leaves extract of nerium in different solvents has different activity [126]. Smith *et al.* tested a hot aqueous extract of *N. oleander* leaves against the treatment of the tumor and observed that it can be useful to inhibit the growth of fibroblast factor-2 [127]. On the basis of results obtained from the study, it was concluded that *N. oleander* leaves have anti-tumor activity. Another team of Erdemoglu studied medicinal capacity of leaves and flower of *N. oleander* and found that both leaves and flower have anti-inflammatory activity against paw edema in mice without causing any gastric damage [128]. Further, Rout *et al.* proved that leaf extract of *N. oleander* inhibited CNS depressant activity in tested animal models [129]. Moreover, macerated leaves of oleander have been used topically to treat baldness, dermatitis, syphilis, and cancers [130].

CONCLUSION

Medicinal plants have continued to contribute to the main sources of medications for a very long time. Numerous medicines are results either directly or indirectly from plant products. In the past decade, research in medicinal plants has been intensified due to the scientific evaluation of traditional drugs to cure various diseases. Frankincense holds the primary position among the medicinal plants of the Dhofar region in terms of exploration of its active constituents. The anti-inflammatory, anti-arthritic, antiproliferative, anti-microbial, and analgesic effect of its gum resin can reduce inflammation and pain in the body and relieve related symptoms of many diseases. Recently, scientists are focusing on anti-cancer properties of gum resin obtained from various species of frankincense and other secondary metabolites obtained from different medicinal plants. Wide-ranging studies on frankincense and other medicinal plants could be proved to be a precise method to finding possible new balancing or substitutive natural medicines to regulate, treat or avoid various diseases.

AUTHOR'S CONTRIBUTION

All authors significantly contributed in this review.

CONFLICT OF INTERESTS

Authors declare they have no conflict of interests.

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