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Ethnopharmacological knowledge for management of oral mucositis in Zahedan, Southeast Iran

Short title: Ethnopharmacological knowledge of oral mucositis in Zahedan

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Abstract
Objectives: Oral mucositis is one of the complications of cancer therapy, which affects the quality of life and imposes remarkable financial costs for patients with cancer. This study aimed at exploring, preserving and scientific investigating of ethnomedicinal knowledge of traditional healers for treatment of oral mucositis, in Zahedan, Iran.
Materials and methods: Field surveys were performed from September 2018 to October 2018 in Zahedan. The data was collected through a structured questionnaire in Persian. All species recorded for the treatment of oral mucositis were sampled. The samples were identified by a botanist, and a voucher specimen of them was deposited in the Herbarium Center of the Faculty of Pharmacy in Kerman, Iran. The needed information, such as scientific name, family, local name, the parts used, and preparation method were also provided. Literature review on the available data on the effect of addressed plant species on mucositis and other relative pharmacological actions such as wound healing and anti-inflammatory properties was done.
Results: In total, 29 informants (Attars) were interviewed, and 18 medicaments were recommended, of which three samples had the synthesis or mineral origin and 15 samples have the herbal origin. Drugs were administered both topically and orally. According to recent studies, two herbs were evaluated for their direct effect on mucositis. Some pharmacological properties related to mucositis treatment by the other 11 samples have been confirmed.
Conclusions: This study provides the characteristics of medicinal plants based on ethnopharmacological knowledge along with their pharmacological properties from Zahedan, Iran, on mucositis treatment.

Keywords
Mucositis; Ethnopharmacology; Traditional medicine; Medicinal plants; Zahedan.

1. Introduction

Oral mucositis is one of the serious complications secondary to cancer therapy [1]. About 20 to 40% of patients who underwent conventional chemotherapy, 80% of patients undergoing high dose chemotherapy due to hematopoietic stem cell transplantation and nearly all patients receiving radiotherapy due to the head and neck cancer may present oral mucositis [2-4]. Mucositis has been described as the inflammation of the mucosa, resulting from mucotoxic cancer therapy either via chemotherapy or radiation. It is known as erythema and/or ulceration of mucosa, which may be induced by trauma or secondary infections [1, 5]. Mucositis not only affects the quality of life in patients with cancer, but it also imposes remarkable financial costs. More than 75% of patients receiving head and neck radiotherapy usually experience severe pain and burning sensation in their mouths, leading to the difficulty in chewing and swallowing, and at last several problems in their dieting [6]. In addition, oral diseases are expensive to treat and sometimes inaccessible [7].

According to the World Health Organization (WHO), most people in developing countries tend to medicinal plant resources, due to their accessibility, effectiveness, and fewer complications. Iran is an ancient Asian country with a great history of medicine thousands of years ago [8]. Ancient Iranian medicine based on humoral theory was a global medical paradigm during medieval times [9]. Despite the replacement of traditional Persian medicine with modern medicine in academia from the 19th century, ethnomedicine with its potent traditional history is still very usual among Iranian people [8, 10], for instance, a study demonstrated that 62.5% of the urban population in Isfahan utilize at least one of the traditional and complementary medicine methods [11]. Peoples in different parts of Iran use medicinal plants for the management of their diseases due to ethnic culture and their own ethno-knowledge. For example, a study on the ethnobotany of Khabr and Rouchon region in Kerman province, Iran showed that the native people utilize 50 medicinal plant species for the alleviation of different disorders, especially for their gastrointestinal problems [12]. It has been shown that more than 77 medicinal plant species have been used by the elderly in Sirjan city, Iran, of which the plants with, therapeutic effects on the respiratory tract have been more considered [13]. Traditional healers named as “Attar” who works in traditional herbal shops named “Attari” are as the most common way to access ethno-medicine services in Iran [8, 10]. Attars are individuals who are prescribing and selling medicinal herbs and natural drugs, whose (most of them) information on herbal medicine is achieved via older generations (verbally), their own experiences, and traditional medicine cultures. These resources can potentially be considered as a mine for introducing medicinal herbs to achieve new drug discovery after scientific research. Recording ethno-knowledge of these traditional healers using ethno-pharmacological techniques can help to prevent such non-written information to be lost after their deaths [14, 15].

Several studies and literature on ethno-pharmacological knowledge of Iranians population have been published [8, 14]; however, to the best of our knowledge, no report in this regard has been found in Zahedan. On the other hand, there is a necessity to explore and preserve the ethnoknowledge by documenting the herbs and natural products that traditionally have been applied in folklore medicine. In this respect, this ethnobotanical study was designed to collect natural products and herbs which are practically used for the treatment of oral mucositis in Zahedan, Southeast Iran, and to evaluate them by applying the current medical concept and

recent scientific studies. We also aimed at highlighting weaknesses in the current knowledge and suggesting future studies.

2. Materials and methods

2.1 Study area

Zahedan is the capital city of Sistan and Baluchestan (SB) province, the widest province of Iran, located in the south-east of the country. It has a common international border (187502 km^2) with Afghanistan and Pakistan at east and south-east, and also a common maritime boundary in the northern coast of the Oman Sea. Kerman and Hormozgan provinces are located in the west and South Khorasan province is located at the north of SB (Fig. 1).
SB province consists of two distinct regions that are naturally different from each other and has a varied herbal flora: 1. Baluchestan is located in the Southern part of the province with diverse climates tied to the Oman Sea. 2. The Northern parts of the Province are named Sistan, which are characterized by the Hirmand River, and Hamun which is a large freshwater lake [16].
Shahr-e Sukhteh is an archaeological site ("Burnt City") from the third millennium BC, is located 154 kilometers far from Zahedan, with considerable evidence on the advanced ancient medicine, which can be regarded as an honored record of this area of Iran [17, 18] (Fig. 2).
Climatic diversity resulting in unique vegetation, areas around, and trade relations with Afghanistan, Pakistan and India (through the sea), the ancient history of medicine and great traditional physicians, such as Hakim Azam Khan (Nazim Jahan) in the 19th century [19, 20], have made this region rich and noteworthy in traditional medicine and ethno-medicine. Zahedan, similar to many other capitals has its attractions compared with other cities in the province, so several immigrants from other cities of the province have been gathered in this city. Using traditional medicine is a common experience among people living in Zahedan and they take the advantages of both native and non-native herbs for treating diseases. This city with 31250 km^2 area is located between latitude: 29°29'46.68"N and longitude: 60°51'46.44"E. It mostly enjoys the warm and dry weather through the year. It has hot days and very low-temperature nights in summer. The average annual rainfall is 120 mm. Its height from the sea level is 1385 m, and it is comprised of about 672589 people.

2.2 Ethnopharmacological investigation and data collection

The protocol of this research has been approved by the ethics committee of Kerman University of medical sciences (code: IR.KMU.REC.1399.023). This study was carried out from September to October 2018. Face to face interview with traditional healers was done, and the structured questionnaires were filled out. First, the personal information of traditional healers (attar), including age, sex, education, the source of their information was taken. The subjects were asked to explain which traditional remedies can help patients with "oral mucosa inflammation (relatively characterized by erythema and pain of mucosa) with/without ulcer". All needed information, including their local name, part(s) used, preparation and administration methods were collected.

2.3 Identification

A sample of all reported traditional drugs was collected from their habitat and transferred to the Department of Pharmacognosy, Faculty of Pharmacy, Kerman University of Medical Sciences, and a voucher code was assigned for each sample as mentioned in the result section.
The information is systematically shown in Table 1.

2.4 Data analysis and literature review survey

The next step was to investigate the studies on the intended plants, especially those associated with mucositis and the relative pharmacological properties published in Scopus and Pubmed

databases (Table 2). So the scientific name of plants and the following keywords were searched:

1. Mucositis
2. Antibacterial, anti-bacterial, antimicrobial, antibacterial activity
3. Antifungal
4. Wound, ulcer wound healing, ulcer protection
5. Inflammation, anti-inflammatory
6. Pain, analgesia, antinociceptive, anti-nociceptive, analgesic

3. Results

3.1 Information from herbal practitioners

Of the 36 traditional herbal stores, 29 Attars were volunteered to be interviewed for the study. All healers were male, with the age range of 23 and 68 years, and 55% of them were younger than 40 years old. About 48% of the participants had a below diploma degree, 24% had a high school diploma, and 28% had academic education. 62% of the healers reported that they have obtained information via older generations, 20% by reading traditional medicine & herbal remedies books, 38% had their own experiences, and 17% via the internet (some of the interviewees had more than one source of information).

3.2 Information about traditional remedies

18 medicaments were introduced for the management of oral mucositis (Table 1), of which, 15 samples had herbal, and three samples had synthesis or mineral origin. *Alcea digitata* Alef (11 attars), *Cotoneaster discolor* Pojark (10 attars), *Johare ghermez* which has mineral origin (10 attars) and *Rhazya stricta* Decne (9 attars) were the most recommend species (Fig. 3). About 83% of drugs were native to Iran and the others have transferred from India or Afghanistan to Iran. Three medicaments have been used both topically and orally, 12 medicaments topically, and four medicaments have been used orally. The preparation methods were mostly decoction, dissolving in water, extraction, distillate, maceration, oil and hydrocolloid produced in water (*loab*) and powder.

Searching throughout databases demonstrated that the effect of only two herbs including *Matricaria chamomilla* L. and *Alcea digitata* Alef on mucositis had been directly evaluated. These two studies showed that both of these herbs are effective in mucositis. Different studies on the other 11 herbs were found indicating some related pharmacological activities help to manage mucositis, such as anti-inflammatory, antibacterial, antifungal and wound healing effects. No study was found to prove the effect of *Cotoneaster discolor* Pojark and *Bambusa arundinacea* Willd On mucositis and even their relative pharmacological effects (Table 2).

4. Discussion

Oral mucositis has been described as erythema or/and ulcer of oral cavity mucosa. The proposed pathobiology of mucositis is a complex pathway consisting of five phases. Inflammation is one of the most important and effective factors in the process of mucositis and causes thinning the epithelial layer and inclining the development of ulcers. By the progression of the damage from epithelium into the submucosa, ulceration and oral bacterial colonization can be occurred. Due to this superimposed infection, the condition may get worse. The lesions of oral mucositis are typically very painful, so analgesic agents, especially opioids are required. Healing phase is the last phase of mucositis. This phase begins with signaling from extracellular matrix of submucosa and eventuate to migrating, proliferating and differentiating epithelial cells at the border of the mucosal ulcers [70, 71]. Accordingly, reducing inflammation as an initiator factor plays an important role to control mucositis. In addition, antibacterial and antifungal agents are effective in mucositis treatment by preventing or treating secondary infections. Pain control can also lead to a sense of well-

being in patients and enhance their quality of life. Speeding up the wound healing process by shortening the duration of mucositis can decline mucositis complications.

This study provided the first ethnopharmacological survey, focusing on oral mucositis. The traditional healers applied various preparation methods for different remedies. Maceration is one of the common specific methods for plant extraction where heat is not normally used. Some of the examples cited in the sources or deduced from traditional stores of medicinal plants have only mentioned the extract method and did not mention the type of extraction method in detail. So, extraction is a generic term and contains decoction, infusion, maceration and so on methods. In the distillate method, the plant is heated in water so that the essential oil of the plant enters the water in a few amounts and gives a weak odor to water[72]. In the maceration method as mentioned above, extraction is done without the use of heat[73]. For oil isolation, hydro-distillation method is used using Clevenger apparatus[74] while for powder preparation, the plant is milled and passed through the sieve with definite mesh. Hydrocolloid is extracted using floating the plant in the water and after a definite time, the extract is filtered and dried[75].

The literature review demonstrates that among the 15 recommended herbs, the effectiveness of *Matricaria chamomilla* L. and *Alcea digitata* Alef have been directly evaluated. In a pilot study, the effectiveness of a combination of *Alcea digitata* Alef and *Malva sylvestris* L. was evaluated for prevention of head and neck radiotherapy- induced oral mucositis. A total of 23 patients were divided into the intervention and placebo groups, which received the drug for seven weeks. The WHO scale was used for evaluation of the severity of oral mucositis symptoms, weekly. The results indicated that patients in the placebo group experienced more severe mucositis from the second week, which was significantly different from the herbal drug-treated group ($p < 0.0001$)[21]. A Randomized, controlled, phase II clinical trial has been conducted on the effectiveness of the liquid extract of *Chamomilla recutita* at the dosages of 0.5%, 1%, or 2% in prevention and treatment of oral mucositis in patients undergoing hematopoietic stem cell transplantation. Patients who received the standard care plus mouthwash of *C. recutita* at the 1% dosage showed less incidence, intensity, and duration of oral mucositis compared with the control group [43].

Searching throughout scientific databases revealed that several remedies used for mucositis treatment by traditional healers in Zahedan, have approved pharmacological properties of the remedies. In this study we aimed to categorize the mechanism of actions according to the recent scientific studies as follows:

Plants with anti-inflammatory activities:

Alhagi maurorum Medik. [23], *Caryophyllus aromaticus* L. [26], *Cichorium intybus* L. [30], *Descurainia sophia* (L.) Webb ex Prantl [35], *Linum usitatissimum* L. [38], *Matricaria chamomilla* L. [44], *Myrtus communis* L. [48], *Plantago ovata* Forssk. [54], *Punica granatum* L. [58], *Rhazya stricta* Decne. [63], *Rhus coriaria* L. [66].

Plants with wound healing properties:

Alhagi maurorum Medik. [24], *Cichorium intybus* L. [32], *Linum usitatissimum* L. [41], *Matricaria chamomilla* L. [46], *Myrtus communis* L. [50], *Plantago ovata* Forssk. [56], *Punica granatum* L. [60].

Plants with anti-microbial/anti-fungal effects:

Alcea digitata Alef. [22], *Alhagi maurorum* Medik. [25], *Caryophyllus aromaticus* L. [28, 29], *Cichorium intybus* L. [34], *Fumaria parviflora* Lam. [37], *Linum usitatissimum* L. [42], *Matricaria chamomilla* L. [47], *Myrtus communis* L. [52], *Plantago ovata* Forssk. [57], *Punica granatum* L. [61, 62], *Rhazya stricta* Decne. [64, 65], *Rhus coriaria* L. [68].

Plants with anti-nociceptive properties:

Alhagi maurorum Medik. [23], *Caryophyllus aromaticus* L. [27], *Cichorium intybus* L. [31], *Fumaria parviflora* Lam. [36], *Linum usitatissimum* L. [40], *Matricaria chamomilla* L. [45], *Myrtus*

communis L. [49], *Plantago ovata* Forssk. [55], *Punica granatum* L. [59], *Rhazya stricta* Decne. [63], *Rhus coriaria* L. [67].

Utilization of traditional medicine among the Iranian people has a wide range of 10% to 75% depending on the diversity of populations [76-79]. Considering that the application of traditional medicine in patients with cancer is associated with potential advantages and also the possible risks, the necessity for further studies on herbal remedies has become more important. For example, although antineoplastic properties of many herbs have been approved, the safety of some others is uncertain. The aqueous extracts of *Dioscorea opposita* and *Cistanche deserticola* in both estrogen receptor negative (SKBR3 and MDA-MB-231) and estrogen receptor positive (MDA-MB-361 and MCF-7) breast cancer cells can lead to stimulation of cell viability. but patients with breast cancer in some parts of the world use these two herbs to relieve adverse effects of cancer treatment [80]. Therefore, designing accurate scientific studies on herbal medicines to prepare evidence to advice or forbid said the mentioned remedies are indispensable.

5. Conclusion

Among 18 medicaments used as ethno-medicine to alleviate mucositis in Zahedan, three of them had synthesis or mineral origin. Only two herbs were evaluated for their direct efficacy on mucositis and the others have not yet been tested. Scientific studies have approved the related pharmacological effects of 11 medicaments. Accordingly, they can be regarded as the appropriate candidates for future studies to determine their probable influences on mucositis followed by new drug discovery. However, the fact that the application of traditional medicine may be associated with potential risks requires more scientific investigations.

6. Conflict of interest

All research done by authors and there are no conflicts of interest associated with this publication.

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Fig. 1. The geographic position of the study area (Zahedan)

Fig. 2. The first ocular prosthesis in medical history, belonging to 5000 years ago. It has been discovered in the burnt city (Shahr-e sukhteh) and has been kept in the ancient Iran museum.

The design of this artificial eye is similar to the actual anatomy of the eyes as proof of the designer's knowledge of ocular anatomy. Additionally, there are some radial lines on the eye. To make the "oldest artificial eye," designers have considered aesthetic aspects along with their thought on the visual issue, especially its physics [18].

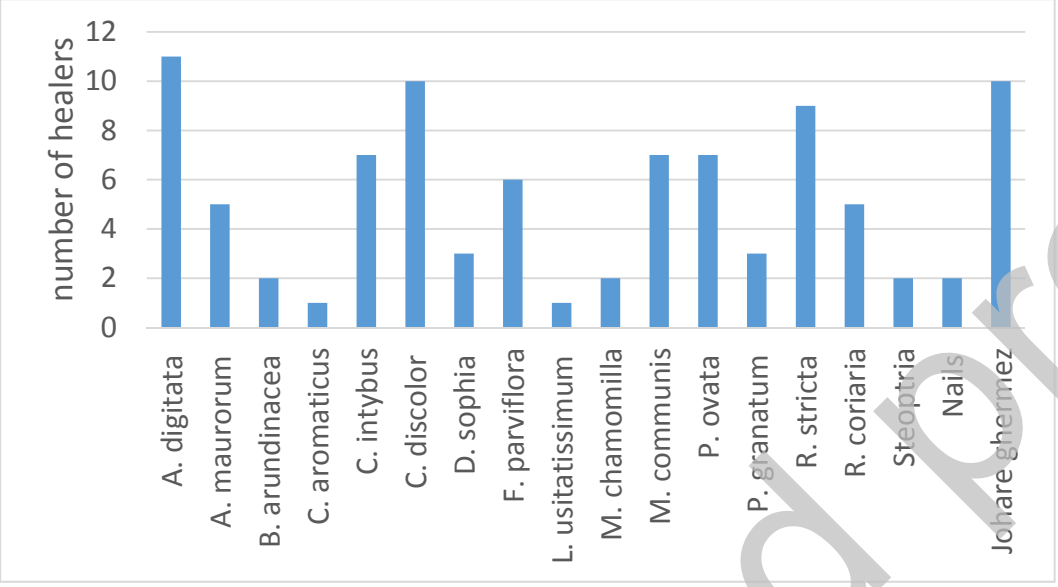

Fig. 3. The number of traditional healers has mentioned the use of each remedy for the treatment of oral mucositis

Table 1. Different remedies for mucositis recommended by traditional healers in Zahedan with their related information.

Local name	**Voucher number**	**N**	**Scientific name**	**Family**	**Part (s) used**	**Habitant**	**Administration**	**Preparation**
Khatmi	KF 1325	11	*Alcea digitata* Alef	Malvaceae	Flower	NI	TO	Decoction
Toranjabin	KF1261	5	*Alhagi maurorum* Medik.	Papilionaceae	Manna	SB	O	Dissolved in water
Tabasheer	KF 1347	2	*Bambusa arundinacea* Willd.	Gramineae	Manna	NN	T	Powder
Mikhak	KF3124	1	*Caryophyllus aromaticus* L.	Myrtaceae	Bud	NN	T	Extract
Kasni	KF1157	7	*Cichorium intybus* L.	Asteraceae	Leave Seed Root	SB	O	Distillate
Shirkhesht	KF1821	10	*Cotoneaster discolor* Pojark	Rosaceae	Manna	NI	TO	Dissolved in water
Khakshir	KF1012	3	*Descurainia sophia* (L.) Webb ex Prantl	Cruciferae	Seed	NI	O	Maceration

Shahtare	KF1235	6	*Fumaria parviflora* Lam.	Fumariaceae	Aerial part	SB	O	Distillate
Katan	KF1253	1	*Linum usitatissimum* L.	Linaceae	Seed	NI	T	Oil
Babune	KF1151	2	*Matricaria chamomilla* L. Syn. *Chamomilla recutita* (L.) Rauschert	Asteraceae	Flower Aerial part	NI	T	Extract
Murd	KF1356	7	*Myrtus communis* L.	Myrtaceae	Leave	SB	T	Distillate Powder
Esfarze	KF1312	7	*Plantago ovata* Forssk.	plantaginaceae	Seed-Husk	SB	T O	Hydrocloid obtain from maceration in water (loab)
Anar	KF1027	3	*Punica granatum* L.	Punicaceae	Flower Peel of Fruit	SB	T	Powder Decoction
Ishrak	KF1167	9	*Rhazya stricta* Decne.	Apocynaceae	Leave	SB	T	Powder
Somagh	KF0931	5	*Rhus coriaria* L.	Anacardiaceae	Fruit	NI	T	Powder
				Origin				
Zaje sefid	KF1281	2	Steoptria	Synthesis		SB	T	Powder
Nile abi	KF1282	2	Nails	Synthesis		SB	T	Powder
Johare ghermez	KF1297	10	Not found any scientific information	Mineral		NN	T	Powder

N: Number of citation, SB: Native to Sistan & Baluchestan province, NI: Native to Iran, but not to Sistan & Balouchestan province, NN: Nonnative to Iran, T: Topical, O: Oral

Table 2. Reported Pharmacological properties in relevance to the ethnomedicinal use of the plants for management of mucositis in Zahedan

No.	Medicinal plants	Plant part preparation	Study design	Main related outcome	Ref.

1	*Alcea digitata* Alef	Flower powder	Human study triple-blind parallel two-armed randomized clinical trial evaluating the effectiveness of *Alcea digitata* Alef and *Malva sylvestris* L. from the beginning of radiotherapy to 2 weeks after the completion of the treatment	↓Mucositis	Rezaeipour 2017[21]
		Ethanolic extract	In vitro Evaluating the effectiveness against Escherichia coli, Klebsiella pneumoniae, Staphylococcus aureus and Streptococcus agalactiae	Antibacterial activity	Zareii 2014[22]
2	*Alhagi maurorum* Medik.	Alcoholic extracts	An animal study (rat) anti-inflammatory activity: using carrageenan-induced rat paw edema method antinociceptive activity: peripherally and centrally using the writhing and the hot plate test	↓Inflammation Algesic property	Awaad 2011[23]
		Aqueous extract	An animal study (rat) evaluating the effectiveness after 21 days treatment of wound site	↑Wound healing	Pourali 2018[24]
		Butanol, ethyl acetate, chloroform, methanol and water extract	In vitro Evaluating the effectiveness against seven bacterial strains and one fungal specie (C. albicans) using disc diffusion susceptibility assay	Antibacterial activity Antifungal activity	Bakht 2014[25]
3	*Bambusa arundinacea* Willd.	None	None	None	None
4	*Caryophyllus aromaticus* L.	Essential oil	An animal study (mice) Evaluating the effectiveness on tongue edema and acute inflammation induced by Dieffenbachia picta Schott	↓Inflammation	Dip 2004[26]
		Flower bud	An animal study (rat) by evaluating central and peripheral analgesic activity by formalin test	Analgesic property	Mathiazhagan 2014[27]

		Essential oil	In vitro Evaluating its effectiveness on bacterial strains isolated from clinical human specimens and foods	Antibacterial activity	Barbosa 2015[28]
		Essential oil	In vitro Evaluating the effectiveness against different Candida species isolated from urine samples	Antifungal activity	Khosravi 2018 [29]
5	*Cichorium intybus* L.	Aqueous seed extract	An animal study (rat) by evaluating expression of hepatic NF-κB and IKKβ and serum TNF-α in streptozotocin and streptozotocin+ niacinamide-induced diabetes in rats	↓Inflammation	Rezagholizadeh 2016[30]
		lactucin and some lactucin-like guaianolides derived from Leaves and roots	An animal study (rat) Evaluating the effectiveness using the hot plate test and tail-flick test	Analgesic property	Wesołowska 2006[31]
		Whole plant and Root methanolic extract, its subextracts, and fractions	An animal study (rat) Evaluating the effectiveness by using in vivo linear incision and circular excision wound models and assessment The hydroxyproline content of the tissues treated with test ointments	↑Wound healing	Süntar 2012[32]
		Ethanolic and methanolic extracts of leaves and roots	In vitro Evaluating the effectiveness by agar well diffusion assay against B. cereus, S. aureus, E. coli, P. aeruginosa,K. pneumonia, A. niger and, P. expansum	Antibacterial activity	Khalaf 2018[33]
		Crude extract and its different solvent soluble fractions (Water a- ethyl acetate – chloroform)	In vitro Evaluating the effectiveness on six bacterial strains and four fungal strains: Aspergillus flavus, Fusariun solani, Aspergillus fumigatus and Aspergillus niger	Antibacterial activity Antifungal activity	Rehman 2014[34]
6	*Cotoneaster discolor* Pojark	None	None	None	None

7	*Descurainia sophia* (L.) Webb ex Prantl	Ethanol extract of seeds	An animal study (rat) using multi-omics analysis for assessment the epigenetic effects	↓Inflammation	Baek 2018[35]
8	*Fumaria parviflora* Lam.	Methanolic extract	An animal study (mice) Evaluating the effectiveness using acute thermal (hot-plate) and persistent chemical (formalin) pain stimuli	Analgesic property	Heidari 2004[36]
		N-octacosan 7β ol compound from Methanolic extract of the whole plant	In vitro Evaluating the effectiveness against Leishmania donovani promastigotes, Staphylococcus epidermidis, Escherichia coli, Candida albicans and, Aspergillus niger	Antibacterial activity Antifungal activity	Jameel 2014[37]
9	*Linum usitatissimum* L.	Dried powder from ethanoic extract of leaves	An animal study (mice) Anti-inflammatory activity: by Xylene test Anti-nociceptive activity: using the hot plate test	↓Inflammation Analgesic property	Rafieian-kopaei 2017[38]
		Gel A mixture of seed oil with Carbomer	Human study Randomized clinical trial Evaluating the effectiveness of gel on symptoms of carpal tunnel syndrome compared with split	↓Inflammation Analgesic property	Setayesh 2017[39]
		Seed powder (in combination with som other seeds)	An animal study (mice) Evaluating the effectiveness using tail flick, hot plate and formalin tests	Analgesic property	Sheibani 2011[40]
		Oil from seeds and then preparation gel form	Animal study (rat) Evaluating the effect of topical gel on the wound healing process, according to histomorphometrical, and stereological parameters	↑Wound healing	Rafiee 2017[41]
		Dried crude (methanol) extract from seeds and also fractionation with different solvents	In vitro Evaluating the effectiveness against Bacillus cereus, Candida albicans, Erwinia carotovora, Escherichia coli, Kleibsiella pneumonia, Salmonella typhi, Pseudomonas aeruginosa, Staphylococcus aureus	Antibacterial activity Antifungal activity	Bakht 2011[42]

10	*Matricaria chamomilla* L. Syn. *Chamomilla recutita* (L.) Rauschert	Mouthwash containing a liquid extract	Human study Randomized, Controlled, Phase II Clinical Trial For evaluating the effectiveness on Prevention and Treatment of oral mucositis in Patients undergoing hematopoietic stem cell transplantation	↓Mucositis	Braga 2015[43]
		Apigetrin (isolated flavonoid)	In vitro investigating the inhibitory effects of apigetrin on neuroinflammation using the BV-2 microglia cell line	↓Inflammation	Lim 2016[44]
		Extract in sesame oil	Human study A randomized, double-blind, placebo-controlled, crossover study Evaluating the effect of topical chamomile oleogel in migraine without aura	Analgesic property	Zargaran 2018[45]
		Fluid extract ointment 10%	An animal study (rat) Evaluating the effect of ointment on wounds inflicted on the rats tongue	↑Wound healing	Duarte 2011[46]
		Essential oil and methanol extract	In vitro Evaluating the effectiveness against bacterial and fungal strains using a broth microdilution method	Antibacterial activity Antifungal activity	Abdoul-Latif 2011[47]
11	*Myrtus communis* L.	Essential oil from Aerial parts	An animal study (mice) evaluating the effectiveness by the carrageenan-induced paw edema test	↓Inflammation	Touaibia 2017[48]
		Essential oil of Leaves	An animal study (mice) Evaluating the effectiveness by using acetic acid-induced writhing test	Analgesic property	Mubarak 2012[49]
		Ethanol extract of leaves	In vitro Description of some molecular mechanisms involved in the angiogenic and wound healing process	↑Wound healing	Raeiszadeh 2018[50]
		Ethanolic extract of seed	An animal study (rat)	↑Wound healing	Hashemipour 2017[51]

			Evaluating the effectiveness on the oral ulcer recovery process		
		Essential oil of leaves	In vitro Evaluating the effectiveness against Bacillus subtilis, Staphylococcus aureus and, Candida albicans by using a disc diffusion assay	Antibacterial activity Antifungal activity	Anwar 2017[52]
		Methanolic extract of leaves	In vitro Evaluating the effectiveness against Enterococcus Faecalis	Antibacterial activity	Nourzadeh 2017[53]
12	*Plantago ovata* Forssk.	Seed	An animal study (rat)/in vitro evaluating the effectiveness on the colonic inflammatory status, both histologically and biochemically in HLA-B27 transgenic rats fed a fiber-supplemented diet/ testing the interaction between two SCFA (butyrate and propionate) as inhibitors of cytokine production in THP-1 cells	↓Inflammation	Rodríguez-Cabezas 2003[54]
		Bulk agent, Plantago ovata	Human study Randomized clinical trial To determine the usefulness of the bulk agent in reducing postoperative pain and tenesmus after open hemorrhoidectomy	Analgesic property	Kecmanovic 2006[55]
		Aqueous extract of seed	An animal study (rat) Evaluating the effectiveness on microscopic and macroscopic ulcer index in peptic ulcer induced by indomethacin	↑Wound healing	Bagheri 2018[56]
		Ethanolic and methanolic extracts of seed husk	In vitro Evaluating the effectiveness against six Gram-negative and eight Gram-positive bacteria by disc diffusion method. Staphylococcus epidermidis and Staphylococcus aureus were the most sensitive species	Antibacterial activity	Motamedi 2010[57]

13	*Punica granatum* L.	Ethanol extract of flower	In vitro Evaluating anti-inflammatory effect in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages	↓Inflammation	Xu 2017[58]
		Hydro-alcohol fruit extracts	Animal study (rat) Evaluating the effectiveness using thermal stimulus assays (hot plate and tail immersion) and, chemically-induced writhing test	Analgesic property	Nadia 2017[59]
		Flower Extract	An animal study (Wistar rats) Evaluating the effectiveness on wound area, healing time, percentage wound contraction and histopathological characteristics in thermal burn injuries	↑Wound healing	Nasiri 2017[60]
		Peel ethanolic extracts, ethanolic extract 80% and aqueous extract	In vitro evaluating the effectiveness by disk method against Escherichia coli, Pseudomonas aerogenosa and Staphylococcus aureus	Antibacterial activity	Mohamed 2018[61]
		Peel extract	An animal study (rat) against oral candidiasis	Antifungal activity	Bassiri-Jahromi 2018[62]
14	*Rhazya stricta* Decne.	Crude extract	An animal study (mice) Evaluating the effectiveness on dermatitis via intensity score and then histological observations	↓Inflammation Analgesic property	Ahmad 2014[63]
		Aqueous alkaloid, aqueous non-alkaloid, organic alkaloid, organic non-alkaloid and whole aqueous extracts derived from leaves	In vitro Evaluating the effectiveness against several multidrug-resistant, human-pathogenic bacteria, including methicillin-resistant Staphylococcus aureus (MRSA) and extended-spectrum beta-lactamase-positive Escherichia coli	Antibacterial activity	Khan 2016[64]
		Monoterpene indole alkaloids isolated from the plant	In vitro Evaluating the effectiveness against six Candida strains	Antifungal activity	Ahmed 2018[65]

15	*Rhus coriaria* L.	Ethanolic extract	An animal study (mice) Evaluating the effectiveness on retinal ischemia induced by optic nerve crush injury using Fluorescence Molecular Tomography (FMT) for monitoring	↓Inflammation	Khalilpour 2018[66]
		Fruit juice	Human study Evaluating the effectiveness on reducing muscle pain during aerobic exercise in healthy volunteers	Analgesic property	Alghadir 2016[67]
		Crude ethanolic extract	In vitro Evaluating the effectiveness against Bacillus subtilis, Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Candida albicans, and Aspergillus niger	Antibacterial activity Antifungal activity	Ertürk 2010[68]
		Essential oil	In vitro Evaluating the effectiveness against Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and Bacillus subtilis	Antibacterial activity	Zhaleh 2018[69]