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ORIGINAL ARTICLE

Ethnopharmacological Knowledge for Management of Oral Mucositis in Zahedan, Southeast Iran

Zahedan, Güney İran'da Oral Mukositle Mücadele İçin Etnofarmakolojik Bilgi

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ABSTRACT

Objectives: Oral mucositis is among the complications of cancer therapy that affects quality of life and imposes remarkable financial costs for patients with cancer. This study aimed to explore, preserve, and scientifically investigate the 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. Data was collected using a structured questionnaire in Persian. All species recorded for the treatment of oral mucositis were sampled. 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. Information, such as scientific name, family, local name, parts used, and preparation method, were also provided. Literature review on available data on effect of the addressed plant species on mucositis and other relative pharmacological actions, such as wound healing and anti-inflammatory properties, was performed.

Results: A total of 29 informants (attars) were interviewed and 18 medicaments were recommended, of which three samples were of synthesis or mineral origin and 15 samples were of 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.

Conclusion: This study provides information on the characteristics of medicinal plants from Zahedan, Iran based on their ethnopharmacological knowledge and pharmacological properties for mucositis treatment.

Key words: Mucositis, ethnopharmacology, traditional medicine, medicinal plants, Zahedan

ÖZ

Amaç: Oral mukosit hayat kalitesini etkileyen ve kanserli hastalarda belirgin ekonomik giderlere yol açan kanser terapisinin komplikasyonlarından biridir. Bu çalışma Zahedan, İran'da oral mukositin tedavisi için geleneksel tedavi edicilerin etnomedisinal bilgilerini bilimsel olarak araştırmak, saklamak ve incelemeyi amaçlamıştır.

Gereç ve Yöntemler: Alan çalışmaları Zahedan'da Eylül 2018 ve Ekim 2018 arasında gerçekleştirilmiştir. Veriler Perslerden yapılandırılmış bir anket kullanarak toplanmıştır. Oral mukositin tedavisi için tüm türler örneklendirilmiştir. Örnekler bir botanikçi tarafından tanımlanmıştır ve örneklerden alınan bir kısım Kerman İran'da bulunan Eczacılık Fakültesi Herbaryum Merkezi'nde saklanmıştır. Bilimsel isim, aile, yerel isim, kullanılan kısımlar ve hazırlama yöntemleri de sağlanmıştır. Mukosit üzerine kullanılan bitki türleri üzerine var olan veriler ve bitkilerin yara iyileştirme ve antiinflamatuvar özellikleri gibi diğer farmakolojik etkileri ile ilgili literatür değerlendirmeleri gerçekleştirilmiştir.

Bulgular: Toplamda 29 bilgi verici (aktar) ile görüşülmüş ve 3 tanesi mineral kökenli ve 15 tanesi herbal kökenli olmak üzere 18 ilaç önerilmiştir. İlaçlar hem topikal hem de oral uygulanmıştır. Son çalışmalara göre, 2 bitki mukosit üzerindeki doğrudan etkileri için değerlendirilmiştir. Bunların diğer 11 örnekle birlikte mukosit ile ilgili diğer farmakolojik özellikleri onaylanmıştır.

Sonuç: Bu çalışma, Zehedan, İran'daki medisinal bitkilerin mukosit tedavisinde etenofarmakolojik bilgilere ve farmakolojik özelliklerine göre karakteristikleri ile ilgili bilgi sağlamaktadır.

Anahtar kelimeler: Mukosit, etenofarmakoloji, geleneksel tıp, medisinal bitkiler, Zahedan

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INTRODUCTION

Oral mucositis is among the serious complications that are secondary to cancer therapy.[1] Approximately 20%-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 head and neck cancer may present oral mucositis.[2-4] Mucositis is described as the inflammation of the mucosa, which results 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 of patients with cancer but 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 ultimately causing several problems in their dieting.[6] Additionally, oral diseases are expensive to treat and sometimes inaccessible.[7]

According to the World Health Organization (WHO), most people in developing countries tend to use 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 the 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 common 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] People in different parts of Iran use medicinal plants for the management of diseases based on their ethnic culture and ethno-knowledge. For instance, 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 gastrointestinal problems.[12] It is reported that more than 77 medicinal plant species are 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 "Attar", who work in traditional herbal shops, named "Attari", are the most common consultants and practitioners of ethnomedicine services in Iran.[8,10] Attars are individuals who prescribe and sell medicinal herbs and natural drugs, whose (most of them) information on herbal medicine is inculcated from older generations (verbally), personal experiences, and traditional medicine cultures. These resources can potentially form the basis for the use of medicinal herbs in new drug discovery after scientific research. Recording the ethno-knowledge and techniques of these traditional healers can help prevent the loss of such non-written information due to death.[14,15]

Several studies on ethnopharmacological 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. In contrast, there is a need to explore and preserve ethno-knowledge by documenting the herbs and natural products that have been traditionally applied in folkloric medicine. In this regard, this ethnobotanical study was designed to collect natural products and herbs that are practically used for the treatment of oral mucositis in Zahedan, Southeast Iran and to evaluate them by applying current medical concept and recent scientific studies. We also aimed to highlight weaknesses in current knowledge and suggest future studies.

MATERIALS AND METHODS

Study area

Zahedan is the capital city of Sistan and Baluchestan (SB) province, the widest province of Iran, located in the Southeastern region of the country. It has a common international border (187,502 km^2) with Afghanistan and Pakistan at the East and Southeast region, respectively, and also a common maritime boundary in the Northern coast of Oman Sea. Kerman and Hormozgan provinces are located in the West and South, respectively. Khorasan province is located at the North of SB (Figure 1).

SB province consists of two distinct regions that are naturally different from each other and have 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 part of the Province is named Sistan, which is characterized by the Hirmand River, and Hamun, which is a large freshwater lake.[16]

Shahr-e sukhteh is an archaeological site "[Burnt city (BC)" from the third millennium BC and is located 154 kilometers far from Zahedan, with a considerable evidence on the advanced ancient medicine, which can be regarded as an honored record of this area of Iran.[17,18]

The climatic diversity resulting in unique vegetation areas 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 ethnomedicine.

Zahedan, similar to many other capitals, has its attractions compared with other cities in the province. As a result, several



Figure 1. Geographic position of study area (Zahedan)

immigrants from other cities of the province have gathered in this city. Traditional medicine is a common among people living in Zahedan and it takes the advantages of both native and nonnative herbs for treating diseases. This city (31250 km^2 area) is located between latitude 29°29'46.68"N and longitude 60°51'46.44"E. It mostly enjoys a warm and dry weather throughout the year. It has hot days and very low-temperature nights in summer. The average annual rainfall is 120 mm. It has an altitude of 1385 m and is comprised of ~672,589 people.

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 conducted from September to October 2018. Face to face interview with traditional healers was conducted and structured questionnaires were filled. First, personal information of traditional healers (attar), including age, sex, education, and source of their information, was taken. The traditional healers 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 local name, part(s) used, preparation, and administration methods of the remedies, were collected.

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.

Data analysis and literature review survey

The next step was to investigate studies on the intended plants, especially those associated with mucositis and the relative pharmacological properties published in Scopus and Pubmed databases (Table 2). The scientific name of plants and the following keywords were used for the literature search:

1- Mucositis

2- Antibacterial, antimicrobial

3- Antifungal

4- Wound, ulcer wound healing, ulcer protection

5- Inflammation, antiinflammatory

6- Pain, analgesia, antinociceptive, antinociceptive, analgesic

In this research, no specific statistical method was used (except for the cases expressed as percentage).

RESULTS

Information from herbal practitioners

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

Information about traditional remedies

A total of 18 medicaments were introduced for the management of oral mucositis (Table 1), of which 15 samples had herbal origin 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 recommended species (Figure 2). Approximately 83% of the drugs were native to Iran and the others were transferred from India or Afghanistan to Iran. Three medicaments were used both topically and orally, 12 medicaments were used topically, and four medicaments were used orally. The preparation methods were mostly decoction, dissolving in water, extraction, distillation, maceration, oil and hydrocolloid produced in water (loab), and powder.

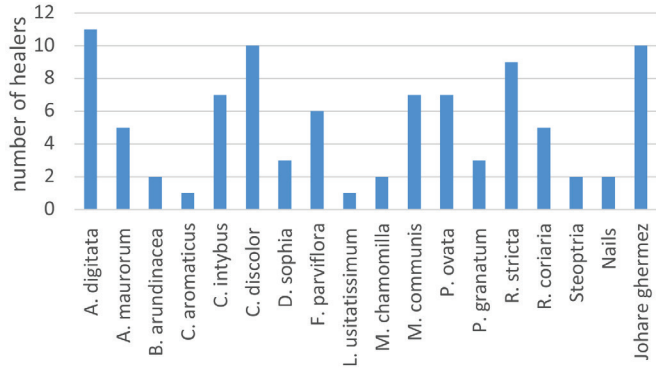


Figure 2. Number of traditional healers that mentioned the use of each remedy for the treatment of oral mucositis

Information obtained via the literature search in various databases reveal the effect of only two herbs, including *Matricaria chamomilla* L. and *Alcea digitata* Alef, on mucositis. These two studies respectively demonstrated that these herbs are effective against mucositis. Different studies on the other 11 herbs indicated some related pharmacological activities for the management of 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, as well as their relative pharmacological effects (Table 2).

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	T O	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	T O	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 and Baluchestan province, NI: Native to Iran, but not to Sistan and Balouchestan province, NN: Non-native to Iran, T: Topical, O: Oral

Table 2. Reported pharmacological properties relevant to ethnomedicinal use of plants for management of mucositis in Zahedan

No	Medicinal plants	Plant part preparation	Study design	Main related outcome	References
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 et al.[21]
		Ethanolic extract	*In vitro* Evaluating the effectiveness against *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus* and *Streptococcus agalactiae*	Antibacterial activity	Zareii et al.[22]
2	*Alhagi maurorum* Medik.	Alcoholic extracts	An animal study (rat) antiinflammatory 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 et al.[23]
		Aqueous extract	An animal study (rat) evaluating the effectiveness after 21 days treatment of wound site	↑Wound healing	Pourali and Yahyaei[24]
		Butanol, ethyl acetate, chloroform, methanol and water extract	*In vitro* Evaluating the effectiveness against seven bacterial strains and one fungal specie (*Candida albicans*) using disk diffusion susceptibility assay	Antibacterial activity Antifungal activity	Bakht et al.[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 et al.[26]
		Flower bud	An animal study (rat) by evaluating central and peripheral analgesic activity by formalin test	Analgesic property	Mathiazhagan et al.[27]
		Essential oil	*In vitro* Evaluating its effectiveness on bacterial strains isolated from clinical human specimens and foods	Antibacterial activity	Barbosa et al.[28]
		Essential oil	*In vitro* Evaluating the effectiveness against different *Candida* species isolated from urine samples	Antifungal activity	Khosravi et al.[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 et al.[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 et al.[31]
		Whole plant and root methanolic extract, its subextracts, and fractions	An animal study (rat) Evaluating the effectiveness 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 et al.[32]

Table 2. Continued

No	Medicinal plants	Plant part preparation	Study design	Main related outcome	References
5		Ethanolic and methanolic extracts of leaves and roots	*In vitro* Evaluating the effectiveness by agar well diffusion assay against *Bacillus cereus*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *A. niger* and, *Penicillium expansum*	Antibacterial activity	Khalaf et al.[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*, *Fusarium solani*, *Aspergillus fumigatus* and *Aspergillus niger*	Antibacterial activity Antifungal activity	Rehman et al.[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 et al.[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 et al.[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 et al.[37]
9	*Linum usitatissimum* L.	Dried powder from ethanoic extract of leaves	An animal study (mice) antiinflammatory activity: By Xylene test Antinociceptive activity: Using the hot-plate test	↓Inflammation Analgesic property	Rafieian-kopaei et al.[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 et al.[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 et al.[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 et al.[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 et al.[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 et al.[43]
		Apigetrin (isolated flavonoid)	*In vitro* Investigating the inhibitory effects of apigetrin on neuroinflammation using the BV-2 microglia cell line	↓Inflammation	Lim et al.[44]

Table 2. Continued

No	Medicinal plants	Plant part preparation	Study design	Main related outcome	References
10		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 et al.[45]
		Fluid extract ointment 10%	An animal study (rat) Evaluating the effect of ointment on wounds inflicted on the rats tongue	↑Wound healing	Duarte et al.[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 et al.[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[48]
		Essential oil of leaves	An animal study (mice) Evaluating the effectiveness using acetic acid-induced writhing test	Analgesic property	Mubarak et al.[49]
		Ethanol extract of leaves	*In vitro* Description of some molecular mechanisms involved in the angiogenic and wound healing process	↑Wound healing	Raeiszadeh et al.[50]
		Ethanolic extract of seed	An animal study (rat) Evaluating the effectiveness on the oral ulcer recovery process	↑Wound healing	Hashemipour et al.[51]
		Essential oil of leaves	*In vitro* Evaluating the effectiveness against *Bacillus subtilis*, *Staphylococcus aureus* and, *Candida albicans* using a disc diffusion assay	Antibacterial activity Antifungal activity	Anwar et al.[52]
		Methanolic extract of leaves	*In vitro* Evaluating the effectiveness against *Enterococcus faecalis*	Antibacterial activity	Nourzadeh et al.[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 et al.[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 et al.[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 et al.[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 et al.[57]

Table 2. Continued

No	Medicinal plants	Plant part preparation	Study design	Main related outcome	References
13	*Punica granatum* L.	Ethanol extract of flower	*In vitro* Evaluating antiinflammatory effect in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages	↓Inflammation	Xu et al.[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 et al.[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 et al.[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 et al.[61]
		Peel extract	An animal study (rat) against oral candidiasis	Antifungal activity	Bassiri-Jahromi et al.[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 et al.[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* and extended-spectrum beta-lactamase-positive *Escherichia coli*	Antibacterial activity	Khan et al.[64]
		Monoterpene indole alkaloids isolated from the plant	*In vitro* Evaluating the effectiveness against six Candida strains	Antifungal activity	Ahmed et al.[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 for monitoring	↓Inflammation	Khalilpour et al.[66]
		Fruit juice	Human study Evaluating the effectiveness on reducing muscle pain during aerobic exercise in healthy volunteers	Analgesic property	Alghadir and Gabr[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[68]
		Essential oil	*In vitro* Evaluating the effectiveness against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Bacillus subtilis*	Antibacterial activity	Zhaleh et al.[69]

DISCUSSION

Oral mucositis has been described as erythema or/and ulcer of the oral cavity mucosa. The proposed pathobiology of mucositis is a complex pathway that involves five phases. Inflammation is among the most important and effective factors in the process of mucositis and it causes the thinning of the epithelial layer and it inclines the development of ulcers. Through progression of the damage from the epithelium into the submucosa, ulceration and oral bacterial colonization can occur. Due to this superimposed infection, the condition may get worse. The lesions of oral mucositis are typically very painful, thus 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 eventuates to migration, proliferation, and differentiation epithelial cells at the border of the mucosal ulcers.[70,71] Accordingly, reducing inflammation as an initiator factor plays an important role in the control of mucositis. Additionally, antibacterial and antifungal agents are effective in mucositis treatment, since they prevent or treat 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 among 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 only mentioned the extract method, but failed to provide details of the extraction method. Thus, extraction is a generic term and it involves decoction, infusion, and maceration, among other methods. In 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 the water.[72] In maceration method, as mentioned above, extraction is done without the use of heat.[73] For oil isolation, hydro-distillation method is done using Clevenger apparatus,[74] while for powder preparation, the plant is milled and passed through a sieve with definite mesh. Hydrocolloid is extracted by floating the plant in 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 intervention and placebo groups that received the drug for 7 weeks. The WHO scale was used for evaluation of 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 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 1% dosage showed less incidence, intensity, and duration of oral mucositis when compared with the control group.[43]

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

Plants with antiinflammatory 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] and *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] and *Punica granatum* L.[60]); plants with antimicrobial/antifungal 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] and *Rhus coriaria* L.[68]); and plants with antinociceptive 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] and *Rhus coriaria* L.).[67]

Utilization of traditional medicine among Iranian people has a wide range of 10-75%, depending on diversity of populations.[76-79] Considering that the application of traditional medicine in patients with cancer is associated with potential advantages and possible risks, the necessity for further studies on herbal remedies has become more pertinent. For instance, although the antineoplastic properties of many herbs have been approved, the safety of some other herbs is uncertain. Administration of 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. However, patients with breast cancer in some parts of the world use these two herbs to relieve the adverse effects of cancer treatment.[80] Therefore, designing accurate scientific studies on herbal medicines to provide evidence to advice or forbid the mentioned remedies are indispensable.

CONCLUSION

Among the 18 medicaments used as ethnomedicine to alleviate mucositis in Zahedan, three of them had synthesis or mineral origin. Only two herbs were evaluated for their direct efficacy against mucositis, while the others have not yet been tested. Scientific studies have approved the related pharmacological effects of 11 medicaments. Accordingly, they can be regarded as

appropriate candidates for future studies on the determination of their probable influences on mucositis, followed by the discovery of new pharmacologic agents. However, the fact that the application of traditional medicine may be associated with potential risks instigates more scientific investigations.

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