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

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

**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, Iran’da oral mukositin tedavisi için geleneksel tedavi edicilerin etnomedisinal bilgilerini bilimsel olarak araştırarak, 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 öne çıkmaktaydı. Örnekler bir botanikçi tarafından tanımlanmıştır ve örneklemler genel olarak bir kısım Kerman Iran’da bulunan Eczacılık Fakültesi Herbaryum Merkezi’nde saklanmıştır. Bilimsel isim, aile, yerel isim, kullanılan kısımlar ve hazırlanma yöntemleri de sağlanmıştır. Mukosit üzerine kullanılan bitki türleri üzerine var olan veriler ve bitkilerin yara iyileştirme ve antiinflamatur propertiesi gibi diğer farmakolojik etkileri ile ilgili literatür değerlendirilmiştir.

**Bulgular:** Toplumda 29 bilgi verici (aktar) ile görüşülmiş ve 3 tanesi mineral kökenli ve 15 tanesi herbal kökenli olmak üzere 18 ilaç önerilmiştir. İlaçların hem topikal hem de oral uygulanmıştır. Son çalışmalarla göre, 2 bitki mukosit üzerindeki doğrudan etkileri için değerlendirilmiştir. Bunların diğer 11 örnekleri birlikte mukosit ile ilgili diğer farmakolojik özellikleri onarlanmıştır.

**Sonuç:** Bu çalışma, Zahedan, Iran’da medisinal bitkilerin mukosit tedavisi için etnomedisinal bilgilerle farmakolojik özelliklerine göre karakteristikleri ile ilgili bilgi sağlamaktaadır.

**Anahtar kelimeler:** Mukosit, etnomedisinal, geleneksel tip, medisinal bitkiler, Zahedan
INTRODUCTION
Oral mucositis is among the serious complications that are secondary to cancer therapy. 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. 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. 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. Additionally, oral diseases are expensive to treat and sometimes inaccessible.

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. Ancient Iranian medicine based on humoral theory was a global medical paradigm during the medieval times. 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. 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. 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. 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. Traditional healers, named “Attar”, who work in traditional herbal shops, named “Attari”, are the most common consultants and practitioners of ethnomedicine services in Iran. 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.

Several studies on ethnopharmacological knowledge of Iranians population have been published, 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 km²) 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. 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.

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 (Nasim Jahan) in the 19th century 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
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 km² 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.

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).
| 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             | Decoction            |
| Toranjabin | KF1261         | 5  | *Alhagi maurorum* Medik. | Papilionaceae               | Manna        | SB       | O             | Dissolved in water   |
| Tabasheer  | KF 1347        | 2  | *Bambusa arundinacea* Wild. | Gramineae                  | Manna        | NN       | T             | Powder               |
| Mikhak     | KF3124         | 1  | *Coryophyllus aromaticus* L. | Myrtaceae                  | Bud          | NN       | T             | Extract              |
| Kasni      | KF1157         | 7  | *Cichorium intybus* L. | Asteraceae                  | Leave        | SB       | O             | Distillate           |
| Shirkhesht | KF1821         | 10 | *Cotoneaster discolor* Pajork | Rosaceae                  | Manna        | NI       | T             | Dissolved in water   |
| Khakshir   | KF1012         | 3  | *Descurainia sophia* (L.) Webb ex Prantl | Cruciferae | Seed | NI | O | Maceration |
| Shahtare   | KF1235         | 6  | *Fumaria parviflora* Lam. | Fumariciace                  | Aerial part  | SB       | O             | Distillate           |
| Katan      | KF1253         | 1  | *Linum usitatisimum* L. | Linaceae                    | Seed         | NI       | T             | Oil                  |
| Babune     | KF1151         | 2  | *Matricaria chamomilla* L. Syn. Chamomilla recutita (L.) Rauschert | Asteraceae | Flower | 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 | Hydrocolloid 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               |
| 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
| 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 | Rezaei et al. 21 |
|   |                  | Ethanal 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 | 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 |
|   | *Bambusa arundinacea* Willd. | Essential oil, 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 | Bakht et al. 25 |
| 3 | *Caryophyllus aromaticus* L. | Essential oil | An animal study (mice) by evaluating expression of hepatic NF-κB and IKKβ and serum TNF-α in streptozotocin and streptozotocin + niacinamide-induced diabetes in rats | ↓ 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 |
| 4 |                  | 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 | Wesolowska 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 |
| 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 |
| 5  | 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 |
| 8  | 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 |
| 9  | Gel | 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 |
| 9  | Seed powder (in combination with some other seeds) | An animal study (mice) Evaluating the effectiveness using tail-flick, hot-plate, and formalin tests | Analgesic property | Sheibani et al.40 |
| 9  | 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 |
| 9  | 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*, *Klebsiella 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 |
| 10 | 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 | 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 |
|    | *Myrtus communis* L. | Essential oil from Aerial parts | An animal study (mice) evaluating the effectiveness by the carrageenan-induced paw edema test | ↓Inflammation | Touaibia48 |
|    | 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 |
|    | *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 |
| 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] |
| 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. [62] |
|    |                  | 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. [63] |
|    |                  | Monoterpeine indole alkaloids isolated from the plant | *In vitro* Evaluating the effectiveness against six Candida strains | Antifungal activity | Ahmed et al. [64] |
|    | *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. [65] |
|    |                  | Fruit juice | Human study Evaluating the effectiveness on reducing muscle pain during aerobic exercise in healthy volunteers | Analgesic property | Alghadir and Gabr [66] |
| 15 |                  | Crude ethanolic extract | *In vitro* Evaluating the effectiveness against *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Candida albicans*, and *Aspergillus niger* | Antibacterial activity | Ertürk [67] |
|    |                  | Essential oil | *In vitro* Evaluating the effectiveness against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Bacillus subtilis* | Antibacterial activity | Zhaleh et al. [68] |
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).75

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.,52 Linum usitatissimum L.,54 Matricaria chamomilla L.,54 Myrtus communis L.,59 Plantago ovata Forssk.,56 and Punica granatum L.60); plants with antimicrobial/antifungal effects (Alcea digitata Alef.,22 Alhagi maurorum Medik.,23 Caryophyllus aromaticus L.,26 Linum usitatissimum L.),54 Matricaria chamomilla L.,54 Myrtus communis L.,59 Plantago ovata Forssk.,56 and Punica granatum L.60); plants with antinociceptive properties (Alhagi maurorum Medik.,23 Caryophyllus aromaticus L.,54 Chorionium intybus L.,59 Fumaria parviflora Lam.,37 Linum usitatissimum L.,54 Matricaria chamomilla L.,59 Myrtus communis L.,59 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.

Conflicts of interest: No conflict of interest was declared by the authors. The authors alone are responsible for the content and writing of the paper.

REFERENCES

1. Peterson DE, Boers-Doets CB, Bensadoun RJ, Herrstedt J. Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol. 2015;26(Suppl 5):v139-v151.

2. Jones JA, Avritscher EBC, Cooksley CD, Michelet M, Bekele BN, Elting LS. Epidemiology of treatment-associated mucosal injury after treatment with newer regimens for lymphoma, breast, lung, or colorectal cancer. Support Care Cancer. 2006;14:505-515.

3. Vera-Llonch M, Oster G, Ford CM, Lu J, Sonis S. Oral mucositis and outcomes of allogeneic hematopoietic stem-cell transplantation in patients with hematologic malignancies. Support Care Cancer. 2007;15:491-496.

4. Vera-Llonch M, Oster G, Hagiwara M, Sonis S. Oral mucositis in patients undergoing radiation treatment for head and neck carcinoma: risk factors and clinical consequences. Cancer. 2006;106:329-336.

5. Lalla RV, Bowen J, Barasch A, Elting J, Epstein JB, McGuire DB, Migliorati C, Nicolatou-Galitis O, Petersen DE. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2014;120:1453-1461.

6. Duncan GG, Epstein JB, Tu D, Sayed SE, Bezjak A, Ottaway J, Pater J. Quality of life, mucositis, and xerostomia from radiotherapy for head and neck cancers: a report from the NCIC CTG HN2 randomized trial of an antimicrobial lozenge to prevent mucositis. Head Neck. 2005;27:421-428.

7. Fatima A, Ahmad M, Zafar M, Yaseen G, Khan MPZ, Butt MA, Sultana S. Ethnopharmacological relevance of medicinal plants used for the treatment of oral diseases in Central Punjab-Pakistan. J Herb Med. 2018;12:88-110.

8. Bahmani M, Zargaran A. Ethnobotanical medicines used for urinary stones in the Urmia, Northwest Iran. Eur J Integr Med. 2015;7:657-662.

9. Zargaran A, Mehdiyadeh A, Zarshenas MM, Mohagheghzadeh A. Avicenna (980-1037 AD). J Neurol. 2012;259:389-390.

10. Hooper D, McNair JB, Field H. Useful plants and drugs of Iran and Iraq. Chicago; Field Museum of Natural History; 1937.

11. Yekta Z, Zamani AR, Mehdiyadeh M, Farajzadegan Z. Pattern of complementary and alternative medicine use in urban population. J Res Health Sci. 2007;7:24-31.

12. Mohamadi N, Sharififar F, Koochpayeh A, Daneshpajouh M. Traditional and Ethnobotanical uses of medicinal plants by ancient populations in Khab and Roughan Iran. J Appl Pharm Sci. 2015;5:101-107.

13. Sharififar F, Koochpayeh A, Motaghi MM, Amirkhosravi A, Puormohseni Nasab E, Khodasheh V. Study the ethnomedical of medicinal plants in Sirjan, Kerman province, Iran. J Herb Drug. 2010;1:19-28.

14. Nowbandegani AS, Kiumarcy S, Rahmani F, Dokouhaki M, Khademian S, Zarshenas MM, Faridi P. Ethnopharmacological knowledge of Shiraz and Fasa in Fars region of Iran for diabetes mellitus. J Ethnopharmacol. 2015;172:281-287.

15. Heinrich M, Verpoorte R. Statistical tools in ethnopharmacology. J Ethnopharmacol. 2012;139:691-692.

16. https://www.sbportal.ir/fa/aboutostan

17. Dabbagh A, Rajaei S, Golzari SEJ. History of anesthesia and pain in old Iranian texts. Anesth Pain Med. 2014;4:e15363.

18. Moghadas AN. Artificial eye in burnt city and theoretical understanding of how vision works. Iran J Public Health. 2014;43:1595-1596.

19. Kasnavie SMH, Sadeghi SMH, Khameh SMH, Khodadoost M, Bazrafshan A, Kamalinejad M, Jaladat AM, Jafari S, Yasinzadeh MR, Gachkar L. Dietary recommendations in fracture healing in traditional persian medicine: a historical review of literature. J Evid Based Complementary Altern Med. 2017;22:513-517.

20. Motaharifard MS, Jafari Z, Paknejad MS, Oveiszadeh L, Karimi M. Prevention and treatment of constipation in children from the perspective of Iranian traditional medicine. J Integr Med. 2016;14:429-435.

21. Rezaei Pour N, Jafari F, Rezaieizadeh H, Nasserli M, Kamalinejad M, Ghobadi A, Shamisipour M, Zargaran A, Ameri A. Efficacy of a persian medicine herbal compound (Alcea digitata afle) and malva sylvestris l) on prevention of radiation induced acute mucositis in patients with head and neck cancer: A pilot study. Int J Cancer Manag. 2017;10: In Press(In Press):e8642.

22. Zarei B, Seyfi T, Movahedi R, Cheraghi J, Ebrahimis S. Antibacterial effects of plant extracts of Alcea Digitata L., Satureja Bachtiarica L. and Ferulago Angulata L. JBUMS. 2014;16:31-37.

23. Awaad AS, El-Meligy RM, Genawy SA, Atta AH, Soliman GA. Anti-inflammatory, anticoccinfective and antipyretic effects of some desert plants. J Saudi Chem Soc. 2011;15:367-373.

24. Pourali P, Yahyaei B. Wound healing property of a gel prepared by the combination of Pseudomonas aeruginosa alginate and Alhagi maurorum aqueous extract in rats. Dermatol Ther. 2019;32:e12779.

25. Bakht J, Naqash G, Shafi M. In vitro antibacterial and antifungal activity of different solvent extracted samples of Alhagi maurorum. Pak J Pharm Sci. 2014;27:1955-1961.

26. Dip EC, Pereira NA, Fernandes PD. Ability of eugenol to reduce tongue edema induced by Dieffenbachia picta Schott in mice. Toxicon. 2004;43:729-735.

27. Matiazhagan S, Anand S, Parthiban R. Analgesic effect of Caryophyllus aromaticus by formalin test in albino rats. Glob J Pharmacol. 2014;8:120-127.

28. Barbosa LN, da Silva Probst I, Andrade BFMT, Alves FCB, Albano M, de Souza MdLR, Doyama JT, Rall VLM, Júnior AF. In vitro antibacterial and chemical properties of essential oils including native plants from Brazil against pathogenic and resistant bacteria. J Oleo Sci. 2015;64:289-298.

29. Khosrovi AR, Sharifzadeh A, Nikaein D, Almaie Z, Gandomi Nasrabad H. Chemical composition, antioxidant activity and antifungal effects of five iranian essential oils against Candida strains isolated from urinary samples. J Mycol Med. 2015;26(Suppl 5):v139-v151.

30. Rezagholizadeh L, Pourfarjarn Y, Nowrouzi A, Nakjavani M, Maysamie A, Ziamajidi N, Nowrouzi PS. Effect of Cichorium intybus L. on the expression of hepatic NF-κB and IKKβ and serum TNF-α in STZ- and STZ+ nacinamide-induced diabetes in rats. Diabetol Metab Syndr. 2016;8:11.
31. Wesolowska A, Nikiforuk A, Michalska K, Kisiel W, Chojnacka-Wójcik E. Analgesic and sedative activities of lacticin and some lacticin-like guianoloides in mice. J Ethnopharmacol. 2006;107:254-258.

32. Sünart I, Küpeli Akkol E, Keles H, Yesilada E, Sarker SD, Baykai T. Comparative evaluation of traditional prescriptions from Cichorium intybus L. for wound healing: Stepwise isolation of an active component by in vivo bioassay and its mode of activity. J Ethnopharmacol. 2012;143:299-309.

33. Khalaf HA, El-Saadani RM, El-Desouky AI, Abdeldaiem MH, Elmehy ME. Antioxidant and antimicrobial activity of gamma-irradiated chicory (Cichorium intybus L.) leaves and roots. J Food Meas Charact. 2018;12:1843-1851.

34. Rehman A, Ullah N, Ullah H, Ahmad I. Antibacterial and antifungal study of Cichorium intybus. Asian Pac J Trop Dis. 2014;4(Suppl 2):S943-S945.

35. Baek SJ, Chun JM, Kang TW, Seo YS, Kim SB, Seong B, Jang Y, Shin GH, Kim C. Identification of epigenetic mechanisms involved in the anti-inflammatory effects of Descurainia sophia seed extract based on a multi-omics approach. Molecules. 2018;23:2879.

36. Heidari MR, Mandgary A, Enayati M. Antinociceptive effects and toxicity of fumaria parviflora Lam. in mice and rats. Daru. 2004;12:136-140.

37. Jameel M, Islamuddin M, Ali A, Afrin F, Ali M. Isolation, characterization and antimicrobial evaluation of a novel compound N-octacosan 7β-ol, fumaria parviflora Lam. in mice and rats. Daru. 2004;12:136-140.

38. Jameel M, Islamuddin M, Ali A, Afrin F, Ali M. Isolation, characterization and antimicrobial evaluation of a novel compound N-octacosan 7β-ol, fumaria parviflora Lam. in mice and rats. Daru. 2004;12:136-140.

39. Setayesh M, Sadeghpour H, Hosseini S, Sarabandi F, Chavoshi-Nejad M, Mohsenikia M, Yadollah-Damavandi S, Seifaee A, Jangholi E, Eghtedari D, Najafi H, Ashkani-Esfahani S. Effect of topical linum usitatissimum on full thickness excisional skin wounds. Trauma Mon. 2017;22:e64930.

40. Sheibani V, Pournourmohammadi S, Anjomshoae M, Sharififar F. In vivo antinociceptive effect of ghavoot, a traditional nutrient crude drug. Inveni Rapid: Ethnopharmacology. 2011.

41. Rafiee S, Nekouyian N, Hosseini S, Sarabandi F, Chavoshi-Nejad M, Mohsenikia M, Yadollah-Damavandi S, Seifaee A, Jangholi E, Eghtedari D, Najafi H, Ashkani-Esfahani S. Effect of topical linum usitatissimum on full thickness excisional skin wounds. Trauma Mon. 2017;22:e64930.

42. Bakht J, Ali H, Khan MA, Khan A, Saeed M, Shafi M, Islam A, Tayyab M. Antimicrobial activities of different solvents extracted samples of Linum usitatissimum by disc diffusion method. Afr J Biotechnol. 2011;10:19825-19835.

43. Braga FTMM, Santos ACF, Bueno PCP, Silveira RCPP, Santos CB, Bastos JK, Carvalho EC. Use of Chamomilla recutita in the prevention and treatment of oral mucositis in patients undergoing hematopoietic stem cell transplantation: a randomized, controlled, phase II clinical trial. Cancer Nurs. 2015;38:322-329.

44. Lim HS, Kim OS, Kim BY, Jeong SJ. Apigenin from scutellaria baicalensis georgi inhibits inflammation in BV-2 microglia and exerts neuroprotective effect in HT22 hippocampal cells. J Med Food. 2016;19:1032-1040.

45. Zargaran A, Borhani-Haghighi A, Salehi-Marzijarani M, Faridi P, Daneshmouz S, Azadi A, Sadeghpour H, Sakhtehman A, Mohagheghzadeh A. Evaluation of the effect of topical chamomile (Matricaria chamomilla L.) oleogel as pain relief in migraine without aura: a randomized, double-blind, placebo-controlled, crossover study. Neurol Sci. 2018;39:1345-1353.

46. Duarte C, Quirino M, Patrocinio M, Anbinder AL. Effects of Chamomilla recutita (L.) on oral wound healing in rats. Med Oral Patol Oral Cir Bucal. 2011;16:716-721.

47. Abdoul-Latif FM, Mohamed N, Edou P, Ali AA, Djama SO, Obame LC, Bassolé IHN, Dicko MH. Antimicrobial and antioxidant activities of essential oil and methanol extract of Matricaria chamomilla L. from Djibouti. J Med Plant Res. 2011;5:1512-1517.

48. Touaibia M. Composition and anti-inflammatory effect of the common myrtle (Myrtus communis L.) essential oil growing wild in Algeria. Phytotherapy. 2017:1-6.

49. Mubarak SS, Ibrar M, Barkatullah, Muhammad N, Ehsan M. Evaluation of essential oil of myrtus communis leaves for analgesic and gastrointestinal motility profile. Pharmacologyonline. 2012;2:41-45.

50. Raesizadeh M, Esmaeili-Tarzi M, Bahrampour-Juybari K, Nematollahi-mahani SN, Pardakhty A, Nematollahi MH, Mehrabani M. Evaluation the effect of Myrtus communis L. extract on several underlying mechanisms involved in wound healing: An in vitro study. S Afr J Bot. 2018;118:144-150.

51. Hashemipour MA, Lotfi S, Torabi M, Sharifi F, Ansari M, Ghassemi A, Sheikhshohae S. Evaluation of the effects of three plant species (Myrtus Communis L., Camellia Sinensis L., Zataria Multiflora Boiss.) on the Healing Process of Intraoral Ulcers in Rats. J Dent (Shiraz). 2017;18:127.

52. Anwar S, Crouch RA, Awadh Ali NA, Al-Fatimi MA, Setzer WN, Weissjohann L. Hierarchical cluster analysis and chemical characterisation of Myrtus communis L. essential oil from Yemen region and its antimicrobial, antioxidant and anti-colorectal adenocarcinoma properties. Nat Prod. Res. 2017;31:2158-2163.

53. Nourzadeh M, Amini A, Fakoor F, Raooof M, Sharififar F. Comparative antimicrobial efficacy of Eucalyptus galbie and Myrtus communis L. extracts, chlorhexidine and sodium hypochlorite against Enterococcus faecalis. Iran Endod J. 2017;12:205.

54. Rodríguez-Cabezas ME, Gálvez J, Camuesco D, Lorente MD, Concha L, Martin-Augustín O, Redondo L, Zarzuelo A. Intestinal anti-inflammatory activity of dietary fiber (Plantago ovata seeds) in HLA-B27 transgenic rats. Clin Nutr. 2003;22:463-471.

55. Kecmanovic DM, Pavlov MJ, Ceranic MS, Kerkez MD, Rankovic VI, Masirevic VP. Bulk agent of Plantago ovata seed on indomethacin-ulcerated rats. Biomed J. 2018;41:41-45.

56. Bagheri SM, Zare-Mohazabieh F, Momeni-Asl H, Yadegari M, Mirjalili A, Anvari M. Antilucre and hepatoprotective effects of aqueous extract of Plantago ovata seed on indomethacin-ulcerated rats. Biomed J. 2018;41:41-45.

57. Motamed H, Darabpour E, Gholipour M, Seyyed Nejad SM. Antibacterial effect of ethanolic and methanolic extracts of Plantago ovata and Oliveria decumbens endemic in Iran against some pathogenic bacteria. Int J Pharmocol. 2010;6:117-122.

58. Xu J, Zhao Y, Aisa HA. Anti-inflammatory effect of pomegranate flower in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages. Pharm Biol. 2017;55:2095-2101.

59. Nadia Z, Aicha M, Sihem H, Abdelmalik B. In vivo analgesic activities and safety assessment of vitis vinifera L and punica granatum L fruits extracts. Trop J Pharm Res. 2017;16:553-561.
60. Nasiri E, Hosseininehr SJJ, Akbari J, Azadbakht M, Azizi S. The effects of punica granatum flower extract on skin injuries induced by burn in rats. Adv Pharmacol Sci. 2017;2017:3059745.
61. Mohamed Z, Ridha OM, Eddine LS, Rebiai A. Phenolic content, Antioxidant and antibacterial activities of peel extract from Punica granatum L. Res J Chem Environ. 2018;22:9-15.
62. Bassiri-Jahromi S, Pourshafie MR, Ardakani EM, Ehsani AH, Doostkam A, Katarae F, Mostafavi E. In vivo comparative evaluation of the pomegranate (Punica granatum) peel extract as an alternative agent to nystatin against oral candidiasis. Iran J Med Sci. 2018;43:296-304.
63. Ahmad M, Muhammed S, Mejabeen, Jahan N, Jan SU, Qureshi ZUR. Anti-dermatitis, anxiolytic and analgesic effects of Rhazya stricta from Balochistan. Pak J Pharm Sci. 2014;27:481-486.
64. Khan R, Baeshen MN, Saini KS, Bora RS, Al-Hejin AM, Baeshen NA. Antibacterial activities of Rhazya stricta leaf extracts against multidrug-resistant human pathogens. Biotechnol Biotechnol Equip. 2016;30:1016-1025.
65. Ahmed A, Li W, Chen FF, Zhang JS, Tang YQ, Chen L, Tang GH, Yin S. Monoterpane indole alkaloids from Rhazya stricta. Fitoterapia. 2018;128:1-6.
66. Khalilpour S, Behnammanesh G, Suede F, Ezzat MO, Muniandy J, Tabana Y, Ahamed MBK, Tamayol A, Majid AMS, Sangiovanni E, Dell’Agi M, Majid AS. Neuroprotective and anti-inflammatory effects of Rhus coriaria extract in a mouse model of ischemic optic neuropathy. Biomedicines. 2018;6:48.
67. Alghadir AH, Gabr SA. Efficacy of Rhus coriaria (sumac) juice in reducing muscle pain during aerobic exercise. Acta Physiol Hung. 2016;103:231-242.
68. Ertürk Ö. Antibacterial and antifungal effects of alcoholic extracts of 41 medicinal plants growing in Turkey. Czech J Food Sci. 2010;28:53-60.
69. Zhaleh M, Sohrabi N, Zangeneh MM, Zangeneh A, Moradi R, Zhaleh H. Chemical composition and antibacterial effects of essential oil of Rhus coriaria fruits in the West of Iran (Kermanshah). JEP. 2018;21:493-501.
70. Panahi Y, Saadat A, Shadboorestan A, Ahmadi A. An updated review of natural products intended to prevent or treat oral mucositis in patients undergoing radio-chemotherapy. Curr Pharm Biotechnol. 2016;17:949-961.
71. Sonis ST. The pathobiology of mucositis. Nat Rev Cancer. 2004;4:277-284.
72. Yousefi M, Afshari R, Sadeghi M, Salari R. Measurement of methanol and ethanol contents in most commonly used herbal distillates produced by three famous brands. Iran J Public Health. 2018;47:901-907.
73. Gholamhoseinian A, Fallah H, Sharifi-Far F, Mirtajaddini M. The inhibitory effect of some Iranian plants extracts on the alpha glucosidase. Iran J Basic Med Sci. 2008;11:1-9.
74. Sharififar F, Moshafi M, Mansouri S, Khodasenas M, Khoshroodi M. In vitro evaluation of antibacterial and antioxidant activities of the essential oil and methanol extract of endemic Zataria multiflora Boiss. Food Control. 2007;18:800-805.
75. Beikzadeh S, Peyghambardoust S, Homayouni RA, Beikzadeh M. Effects of psyllium and marve seed mucilages on physical, sensory and staling properties of sponge cake. J Agr Sci Tech. 2017;19:1079-1089.
76. Kashani L, Hassanzadeh E, Mirzabeighi A, Akhoundzadeh S. Knowledge, attitude and practice of herbal remedies in a group of infertile couples. Acta Med Iran. 2013;51:189-194.
77. Roozbeh J, Hashempur MH, Heydari M. Use of herbal remedies among patients undergoing hemodialysis. Iran J Kidney Dis. 2013;7:492.
78. Sattari M, Dilmahghanizadeh M, Hamishehkar H, Mashayekhi SO. Self-reported use and attitudes regarding herbal medicine safety during pregnancy in Iran. Jundishapur J Nat Pharm Prod. 2012;7:45.
79. Tabatabaei M. Use of herbal medicine among pregnant women referring to Valiasr Hospital in Kazerou, Fars, South of Iran. J Med Plants Res. 2011;1:96-108.
80. Yue GGL, Wong LS, Leung HW, Gao S, Tsang JYS, Lin ZX, Tse GMK, Lau CBS. Evaluation of the safety profiles of estrogenic Chinese herbal medicines in breast cancer. Phytomedicine. 2019;56:103-117.