Research Journal of Pharmacognosy (RJP) 7(1), 2020: 77-84
Received: 13 May 2019
Accepted: 13 Nov 2019
Published online: 1Dec 2019
DOI: 10.22127/rjp.2019.185587.1496

Review article

Citrullus colocynthis: the Most Suggested Herb in Persian Medicine for Management of Low-Back Pain

Mohamad Sanei[1], Roshanak Mokaberinejad[1*], Farzin Roozafzai[2], Shobeir Rostami Abousaidi[3]

[1]Department of Traditional Medicine, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[2]Digestive Diseases Research Institute, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.
[3]Department of Orthopedics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Abstract

Low-back pain is a common disease and a considerable economic burden in modern societies. Complementary and alternative therapies for assisting management of pain and disability are sought by a large number of patients. In the present work, the most common herbs used to manage Low-back pain in Iranian traditional medicine (Persian medicine) and current literature has been investigated. Chapters about low-back pain ("Vaja-e Zahr"), and radiculopathy ("Erghonnasa") and sciatica from Liber Continens (Alhavi) and Canon of Medicine were reviewed. All types of plant usage mentioned in the books including oral, rectal, and topical administration, either alone or in combination were recorded. Descriptive statistics (frequency distributions) were used to report the findings. The current literature were searched with "herbal medicine" and "low-back pain" medical subject heading (MeSH) terms in PubMed, EMBASE, ScienceDirect, Scientific Information Database (in Persian), and Google Scholar databases, to investigate medicinal usage of the most suggested plants. *Citrullus colocynthis* L. Schrad was the most common plant that Rhazes used in compounds and a significant herb used by Avicenna for management of low-back pain and sciatica. Fruit was the main part and rectal route was the main type of administration of colocynth for low-back pain management. In conclusion, we have proposed a new use of *Citrullus colocynthis* for management of low-back pain and sciatica according to the evidences from Persian medicine. According to current literature survey, no study has yet investigated or suggested the usage of *Citrullus colocynthis* for low-back pain management. Further laboratory and clinical studies are required to confirm the safety and efficacy of this plant or its components in low-back pain and sciatica management.

Keywords: *Citrullus colocynthis*; herbal medicine; low back pain; Persian medicine; traditional medicine

Citation: Sanei M, Mokaberinejad R, Roozafzai F, Rostami Abousaidi Sh. *Citrullus colocynthis*: the most suggested herb in Persian Medicine for management of low-back pain. Res J Pharmacogn. 2020; 7(1): 77-84.

Introduction

Reported by the global burden of diseases (GBD) disability-adjusted life-years (DALY) and Injuries and Healthy Life Expectancy (HALE) Collaborators, worldwide all-age DALY for low-back pain counted to 72.3 million in 2013 [1]. The one-month and lifetime prevalence of LBP is estimated to be 35-37% and 70-85%, respectively; and it is the most prevalent in people aged 45-59 years [2,3]. Despite several diversified treatments

*Corresponding author: mokaberi@sbmu.ac.ir

available, low-back pain management still has remained with high prevalence of failure[4].

In a survey conducted by World Health Organization, 70-80% of world's population rely on nonconventional and herbal medicine in their primary health care. Traditional medicinal plants are used to develop significant drugs and biological active compounds [5]. Research in complementary and alternative medicine has been amplified in the past 20 years and many traditional treatments, such as traditional massage techniques and herbal treatments are suggested for the condition [6]. Iranian traditional medicine (Persian medicine) has a history of over 7000 years [7]. Abu Bakr Muhammad ibn Zakariya Razi (865-925 AD), also known as Rhazes, and Abu Ali Al-Hossein Ibn Abdullah Ibn-e-Sina (980-1037 AD), known as Avicenna, were the two greatest physicians of history [7,8]. "Alhavi fi-Al-teb" known as Liber Continens by Rhazes, and Canon of Medicine by Avicenna are the most complete references of Iranian traditional medicine [9-12].

Both mentioned books were reviewed to find the most common plants used in traditional Persian remedies for management of low-back pain and sciatica, and compared with recent evidences from conventional medicine.

Methods

Persian medicine is a 10000 years old science with several sources [13]. Two books of Canon of Medicine and Liber Continence were selected as the most well-known references of Persian medicine to execute a simple manual text data mining to find the most common plants in compounds for management of low back pain and sciatica that Rhazes and Avicenna have disclosed. Consequently, the main plants in modern literature for usage in low-back pain management were investigated.

Chapters about low-back pain "Vaja-e zahr", and radiculopathy and sciatica "Erghonnasa" from Liber Continens and Canon of Medicine were reviewed in this study. All types of plant administration including oral, rectal (enema and suppository), and topical usage, either solely or in compounds were recorded to find the most mentioned herbs used to manage low-back pain and sciatica. All compounds were added to the data sheet manually, and double-checked by two different authors. The third check was done by searching the plant names from the data sheet, through the chapters by using Microsoft word "find" tool. The plants that were mentioned for any other reason than management of low-back pain or sciatica were omitted manually.

The data was gathered in MS Excel datasheets (Microsoft, USA), and was analyzed by IBM SPSS v.22 (IBM, USA). Descriptive statistics (frequency distributions) was used to report the findings. The scientific names of the plants were matched with "Dictionary of Iranian plants names" and "Matching the old description of medicinal plants with the scientific ones " [14,15]. After finding the most common plants in traditional literature, current literature was also searched for plant use for low-back pain, with "herbal medicine", "Medicinal herb" and "low-back pain" medical subject heading (MeSH) terms in PubMed, EMBASE, ScienceDirect, Scientific Information Database (Persian), and Google Scholar databases.

Results and Discussion

Table 1 shows the frequency distribution of medicinal herbs suggested for management of low-back pain and sciatica in traditional literature. The herbs mentioned less than 10 times were not reported. *Citrullus colocynthis* was the most common herb used in Iranian traditional medicine (Persian medicine) for treatment of low-back pain and sciatica (n=41). Rhazes mentioned *Citrullus colocynthis* in 31 remedies that was described in Liber Continents. The next two common plants suggested by Rhazes were *Vitis vinifera* (n=28) and *Centaurea centaurium* (n=17). Avicenna, as well, mostly suggested *Citrullus colocynthis* (n=10), and *Anacyclus pyrethrum* (n=8) for low-back pain management.

Herbs suggested as treatments of choice "Mojarrabat" for management of low-back pain and sciatica in both mentioned books have been shown in table 2. Treatments of choice "Mojarabat" are the plants or materials that are highlighted by the authors that are more effective in treatment of the condition. *Citrullus colocynthis* (11/93), *Vitis vinifera* (as wine and vinegar) (6/93) and honey (5/93) were the most used herbal ingredients in remedies of choice. Table 3 represents different types of administration of *Citrullus colocynthis*, suggested by Iranian traditional medicine (Persian medicine)

for management of low-back pain and sciatica.

Table 1. Herbs mentioned for management of low-back pain in two Persian medicine references

Scientific name	Common name	Traditional name	Liber Continens [a]	Canon of Medicine [a]	Total [a]
Citrullus colocynthis L. Schrad	Bitter Apple	"Hanzal"	31	10	41
Vitis vinifera L.	Grape Vine	"Angoor" (Sharab/Serke")	28	4	32
Centaurium cyanus L.	Centaury	"Quanturyun"	17	5	22
Anacyclus pyrethrum L.	Pellitory	"Akarakara"	10	8	18
Lepidium latifolium L.	Pepperweed	"Sheytaraj"	12	5	17
Lepidium campestre L.	Garden cress	"Tare-tizak"	13	2	15
Colchicum autumnale L.	Meadow saffron	"Soorenjaan"	9	4	13
Capparis spinosa L.	Caper bush	"Kabar"	12	1	13
Ruta graveolens L.	Rue	"Sodaab"	7	5	12
Sinapis arvenesis L.	mustard	"Khardal"	8	4	12
Ferula persica Willd.	Sagapenum	"Sakbinaj"	11	1	12
Saussurea costus L.	Costus	"Qost"	6	5	11
Commiphora myrrha Engl.	Myrrh	"Morr"	7	4	11
Olea europaea L.	Olive	"Zeytoon"	8	3	11
Cuminum cyminum L.	Cumin	"kammoon"	6	5	11
Trigonella foenum-graecum L.	Fenugreek	"Holbah"	9	1	10

[a] Numbers represent the count of times the plants were mentioned.

Table 2. Treatments of choice "Mojarabat" for low-back pain in Persian medicine references.

Scientific name	Traditional name	Liber Continens [a]	Canon of Medicine [a]	Total [a]
Citrullus colocynthis L. Schrad	Hanzal	9	2	11
Vitis vinifera L.	"Angoor" "(Sharab/Serke)"	4	2	6
Honey	"Asal"	4	1	5
Anacyclus pyrethrum L.	" Akarakara "	2	1	3
Centaurium cyanus L.	"Qanturyun"	2	1	3
Colchicum autumnale	"Soorenjaan"	1	2	3
Lepidium campestre L.	"Tare-tizak"	3	0	3
Helleborus niger L.	"Kharbagh-e siah"	2	1	3
Trigonella foenum-graecum L.	"Holbah"	2	1	3
Euphorbia lathyris L.	"Farfiyun"	1	1	2
Cuminum cyminum L.	" kammoon "	1	1	2
Olea europaea L.	"Zaytoon"	2	0	2
Capparis spinosa L.	"Kabar"	2	0	2
Artemisia pontica L.	"Shih"	2	0	2
Lepidium latifolium L.	"Sheytaraj"	2	0	2
Iris florentina L.	"Irsa"	2	0	2
Ferula asafetida L.	"Angdan"	2	0	2
Delphinium staphysagria L.	"Mavizak"	2	0	2
Cassia fistula L.	"Floos"	2	0	2
Astragalus sarcocolla Dym.	"Anzaroot"	1	0	1
Lawsonia alba Lam.	"Henna"	1	0	1
Asarum europaeum L.	"Asaroon"	1	0	1
Peganum harmala L.	"Espand"	1	0	1
Artemisia absinthium L.	"Afsantin"	1	0	1
Mentha pulegium L.	"Foodanaj"	1	0	1
Thapsia garganica	"Tafsia"	1	0	1
Lupinus angustifolius L.	"Tormes"	1	0	1
Ruta graveolens L.	"Sodaab"	1	0	1
Ferula persica Willd.	"Sakbinaj"	1	0	1
Thymus serpyllum L.	"Sa'tar"	1	0	1
Laurus nobilis L.	"Ghaar"	1	0	1
Piper nigrum L.	"Folfol-e Siah"	1	0	1
Vicia ervillia Wi.	"Karsanah"	1	0	1
Gypsophila struthium L.	"Kondos"	1	0	1
Coriandrum sativum L.	"Kozborah"	1	0	1
Daphne mezereum L.	"Mazariyun"	1	0	1
Anamirta paniculata Colebr.	"Mahi zahre"	1	0	1
Commiphora myrrha Engl.	"Morr"	1	0	1
Origanum majorana L.	"Marzanjoosh"	1	0	1
Commiphora mukul Engl.	"Moghl"	1	0	1
Acorus calamus L.	"Vaj"	1	0	1
Costus amarus Rad.	"Qost"	0	1	1
Anthemis nobilis L.	"Baboone"	0	1	1
Ricinus communis L.	"Kherva"	0	1	1
Convolvulus scammonia L.	"Saqmunyia"	0	1	1
Aloe vera L.	"Sebr"	0	1	1
Populus euphratica L.	"Gharab"	0	1	1
Polyporus officinalis Fr.	"Gharighoon"	0	1	1
Brassica oleracea L.	"Kornob"	0	1	1

Asparagus officinalis L.	"Halyoon"	0	1	1

[a] Numbers represent the count of times the herbs were mentioned.

Table 3. Suggested uses of *Citrullus colocynthis* for low-back pain management in two Persian medicine references.

Parts of plant	Type of usage	Liber Continents [a]	Canon of Medicine [a]
Fruit	Oral	6	2
	Rectal	6	0
	Topical	6	1
Root	Oral	0	0
	Rectal	1	0
	Topical	0	0
Hull	Oral	1	0
	Rectal	1	0
	Topical	0	0
Not specified	Oral	0	3
	Rectal	9	2
	Topical	1	2
Treatment of choice	Formulation		
No	Compound	13	6
	Alone	9	2
Yes	Compound	7	1
	Alone	2	1

[a] Numbers represent "count" of times the herbs were mentioned.

Fruit was the part mainly used for low-back pain management; root and hull were also used in the remedies. Out of 41 remedies consisting 19, 12, and 10 were administrated rectally (enema and suppository), orally, and topically, respectively. As shown in table 3, Rhazes suggested *Citrullus colocynthis* in 20 compound remedies and mentioned its sole use 11 times; note-worthily, nine of them were treatments of choice, i.e., "Mojarabat". In chapters from Canon of Medicine related to low-back pain and sciatica, Avicenna described six compounds and one remedy made with *Citrullus colocynthis* alone. He introduced two of these remedies as treatments of choice.

PubMed, EMBASE, ScienceDirect, Persian Scientific Information Database, and Google Scholar databases were searched from 1970 to march 2018 and surprisingly, in the current literature of conventional and evidence-based medicines, there were no suggestions of *Citrullus colocynthis* usage for low-back pain or sciatica management

The management of low-back pain is still a very challenging task for physicians and the treatment and/or out of work costs impose heavy burdens on nations [16]. Complementary and alternative medicine is taking place in challenging medical conditions and the trend of herbal treatment is rising worldwide. Herbal medication includes herbal preparations, herbal materials, and herbal products that are consisted of plant active ingredients or plant materials and are applied orally, intravenously, or topically [16]. There are several types of herbal medications reported for management of pain, particularly low-back pain, such as *Capsicum frutescens, Salix alba, Maleluca alternifolia. Commiphora molmol, Menthe peperita, Arnica montana, Angelica sinensis, Aloe vera, Thymus officinalis, Tancaetum parthenium, Harpagophytum procumbens*, and *Zingiber officinalis* [16]. In a systematic review, Gagnier et al. investigated randomized controlled trials for low-back pain management with herbal medicine. They concluded that *Harpagophytum procumbens, Capsicum frutescens*, and *Salix alba* could reduce pain when compared with placebo.

Citrullus colocynthis belongs to the family of cucurbitaceae. It is also known as bitter apple or bitter cucumber, and is named *"*Hanzal*"* in Arabic and "Hendavane Aboujahl" in Persian. It is a perennial or annual herbaceous vine with angular stems; and the size of fruit approximates to an orange [5]. The plant natively grows in desert areas, and is known for its wide range of medicinal and pharmaceutical usage [17]. Chemical constituents of *Citrullus colocynthis* include carbohydrates, proteins and amino acids, tannins, saponins, phenolics, flavanoids, flavone glucosides, terpenoids, alkaloids, anthranol, steroids, cucurbitacins, cardiac glycoloids, trace elements, and many other chemical groups [5]. In "Makhzan-al-adviah", an ancient reference of

Iranian traditional medicine, medicinal herbs are categorized in four levels of strength, among which plants in the level four are the most powerful and toxic ones and need to be prescribed very carefully [18]. *Citrullus colocynthis* is mentioned with strength level 4 in warm effect and level 2 in dry temperament.

The toxicity of *Citrullus colocynthis* is both mentioned in traditional and recent scientific literature. The teratogenicity of *Citrullus colocynthis* pulp extract was studied in rats and results suggested that it may cause teratogenic effect during the first stages of pregnancy [19]. It is also reported that long term exposure of female rats to *Citrullus colocynthi*s may cause adverse effects on fertility and reproductive system [20]. In a case series reported in 2013, four patients with *Citrullus colocynthis* intoxication presented with acute rectorrhagia and bloody diarrhea. Colonoscopy findings showed mucosal erosions which completely resolved in two weeks [21].

Curcurbitacin glycoside content of *Citrullus colocynthis* has a strongly irritating and painful effect on mucus membranes. Bloody diarrhea, vomiting, colic and kidney irritation and increased diuresis which is progressed to anuria are the symptoms of overdose and intake of toxic dosages (0.6 to 1 g). Lethal doses starting at 2 g, lead to convulsions, paralysis and circulatory collapse which may lead to death [22].

Colocynth fruit is known as a severe toxic plant; however the median lethal dose (LD_{50}) in a saponin rich extract has been reported to be 200 mg/kg [17]. Dose adjustment would play a key role in preventing the toxic adverse effects of *Citrullus colocynthis*. In traditional medicine, *Citrullus colocynthis* was mostly used in combination with other medicinal herbs as combined drugs, or might be processed before use which could decrease the toxicity.

The main effects that Rhazes and Avicenna were expecting from *Citrullus colocynthis* were its laxative and purgative effects, which would mainly help to elicit the excessive phlegm and pathologic substances from the involved tissues, and the whole body, by discharge them through the bowel. In Persian traditional medicine, phlegm "Balgham" is one of the four humors in body, which it`s excess and overload is the underlying cause of many diseases such as low back pain. This trait is the main reason that this herb might be useful for management of diseases, such as many types of digestive disorders, liver disorders, neurogenic pains, low back pain and sciatica 18]. Rhazes and Avicenna noticed sciatica as the end stage of low-back pain, in which the pathologic substances were at higher levels and needed to be removed from the body. Therefore, it was not surprising that they prescribed *Citrullus colocynthis* for management of low-back pain and sciatica even more than main traditional musculoskeletal plants, such as *Colchicum autumnale* or *Commiphora mukul*.

Citrullus colocynthis was used solely or in combination with other herbs through oral, rectal, or topical administration [18]. The two references mostly suggested its rectal administration using different forms of this plant, such as oil and extracts. Roots, fruits, leaves, and seeds were its medicinal parts with purgative effects [18]. Both Rhazes and Avicenna mainly used colocynth fruit for management of low-back pain. In recent studies, polar extracts (acetone and methanol extracts) of its fruit and non-polar extracts (petroleum ether extract) of its seed demonstrated the highest anti-inflammatory and analgesic activity in an animal study conducted by Marzouk and colleagues [21].

The current literature of complementary and alternative medicine has not suggested the usage of *Citrullus colocynthis* to manage low-back pain or sciatica [23]. Gerayeli Malek et al. did not mention the use of colocynth for LBP in a review of five medicinal plants used in Iranian traditional remedies [24]. In another review of analgesic and anti-inflammatory substances in Canon of Medicine, the authors did not mention colocynth either [25]. Conventional medicine also presents no evidence for *Citrullus colocynthis* usage for low-back pain or sciatica management. The reason might be the more focus on studying the basic effects of colocynth and not studying its effects on diseases and conditions [6,26]. However, there are evidences of antioxidant [5,27], antibacterial[5,17,28,29], insecticidal[17], anti-diabetic [5,29,30], insulinotropic [31,32], hypolipidemic [5,17], anticonvulsant [33], hepatoprotective [34], immuno-stimulating and anti-cancer[5,29,35], anti-androgenic alopecia [5,36], anti-allergic[17], anti-inflammatory [21,29,37] and anesthetic and analgesic [5, 21,38,39] effects of *Citrullus colocynthis*. We found an emphasis on its usage for management of low-back pain and sciatica in Iranian traditional medicine, which could be a trigger for future observations and interventions,

considering the anti-inflammatory and analgesic effects of this plant.

Regarding the study drawbacks, by reviewing the two major references of Iranian traditional medicine, i.e., Liber Continens and Canon of Medicine, we did not include other sources of Iranian traditional medicine, which may lead to exclusion of other medicinal plants used for L low-back pain BP management.

Conclusions

In the present work, we proposed a new possible use of *Citrullus colocynthis* for management of low-back pain and sciatica according to the evidences from Iranian traditional medicine (Persian medicine). The dose adjustment and safety of the plant or its derived components should be studied in animals. Further human clinical studies are suggested to confirm its efficacy on low-back pain and sciatica management. We would like to suggest the method and use of the traditional medicine literature data mining to find the most possible useful plants for other conditions and to investigate more sources compared to this study.

Acknowledgments

This study was based on Ph.D. thesis of Traditional Medicine (Mohamad Sanei, No.190), granted by School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Author contributions

Mohamad Sanei and Shobeir Rostami Abousaidi reviewed the traditional and current literature and collected the data. Farzin Roozafzai and Mohamad Sanei analyzed the data and drafted the paper. Roshanak Mokaberinejad reviewed the paper and scientifically supervised the process.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

References

[1] Dalys GBD, Collaborators H, Murray CJ, Barber RM, Foreman KJ, Abbasoglu Ozgoren A, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990-2013: quantifying the epidemiological transition. *Lancet*. 2015; 386(10009): 2145-2191.

[2] Andersson GB. Epidemiological features of chronic low-back pain. *Lancet*. 1999; 354(9178): 581-585.

[3] Papageorgiou AC, Croft PR, Ferry S, Jayson MI, Silman AJ. Estimating the prevalence of low back pain in the general population. Evidence from the South Manchester back pain survey. *Spine (Phila Pa 1976)*. 1995; 20(17): 1889-1894.

[4] Hamaguchi T, Yoshino T, Horiba Y, Watanabe K. Goshajinkigan for low back pain: an observational study. *J Altern Complement Med*. 2017; 23(3): 208-213.

[5] Al-Snafi AE. Chemical constituents and pharmacological effects of *Citrullus colocynthis*-a review. *IOSR J Pharm*. 2016; 6(3): 57-67.

[6] Gagnier JJ, Van Tulder MW, Berman B, Bombardier C. Herbal medicine for low back pain: a Cochrane review. *Spine (Phila Pa 1976)*. 2007; 32(1): 82-92.

[7] Choopani R, Sadr S, Kaveh S, Kaveh N, Dehghan S. Pharmacological treatment of catarrh in Iranian traditional medicine. *J Tradit Complement Med*. 2015; 5(2): 71-74.

[8] Nikaein F, Zargaran A, Mehdizadeh A. Rhazes' concepts and manuscripts on nutrition in treatment and health care. *Anc Sci Life*. 2012; 31(4): 160-163.

[9] Changizi Ashtiyani S, Golestanpour A, Shamsi M, Tabatabaei SM, Ramazani M. Rhazes' prescriptions in treatment of gout. *Iran Red Crescent Med J*. 2012; 14(2): 108-112.

[10] Razi M. Liber Continens (Alhavi fi-al-teb). Tehran: Shahid Beheshti Medical University, Traditional Medicine and Materia Medica Research Center, 2016.

[11] Ibn-e-Sina. Canon of Medicine (Al-Qanun fi-al-teb). Beirut: Syndicate of Publishers Union in Lebanon, 2005.

[12] Jafari-Dehkordi E, Mokaberinejad R, Minaei B, Sohrabvand F, Nazem E, Hashem Dabaghian F, Aliasl J. A Review of pioneer physicians' work on maternal health in pregnancy in ancient Iran; narrative systematic review. *Iran J Public Health*. 2013; 42(12): 1340-1346.

[13] Elgood C. A medical history of persia and the eastern caliphate: from the earliest times

until the year A.D. 1932. Cambridge: Cambridge University Press, 2010.
[14] Mozaffarian V. A dictionary of Iranian plant names. 7 ed. Tehran: Farhang Moaser, 2013.
[15] Amin G. Popular medicinal plants of Iran. 2ed. Tehran: Tehran University of Medical Sciences, 2008.
[16] Aghili Alavi Shirazi M. Collection of drugs (Makhzan-al-adviah). Tehran: Bavardaran Press, 2001.
[17] Abdalla Elgerwi A, Benzekri Z, ElMagdoub A, El-Mahmoudy A. Qualitative identification of the active principles in *Citrullus colocynthis* and evaluation of its teratogenic effects in albino rats. *J Basic Clin Pharmacol*. 2013; 2(4): 438-445.
[18] Qazan W, Almasad MM, Daradka H. Short and long effects of *Citrullus colocynthis* L. on reproductive system and fertility in female Spague-Dawley rats. *Pak J Bio Sci*. 2007; 10(16): 2699-2703.
[19] Marzouk B, Marzouk Z, Fenina N, Bouraoui A, Aouni M. Anti-inflammatory and analgesic activities of Tunisian *Citrullus colocynthis* Schrad. zmmature fruit and seed organic extracts. *Eur Rev Med Pharmacol Sci*. 2011; 15(6): 665-672.
[20] PDR for herbal medicines. 2nd ed. Montvale: Medical Economics Company, 2000.
[21] Marlowe D. Complementary and alternative medicine treatments for low back pain. *Prim Care*. 2012; 39(3): 533-546.
[22] Gerayeli Malek V, Abbasian A, Karimi M, Khanlarkhani N, Parvari S. 5 Medicinal plants used in Iranian traditional medicine for low back pain: a quick review. *Euro J Exp Bio.* 2017; 7(4): 1-4.
[23] Mahdizadeh S, Khaleghi Ghadiri M, Gorji A. Avicenna's canon of medicine: a review of analgesics and anti-inflammatory substances. *Avicenna J Phytomed*. 2015; 5(3): 182-202.
[24] Gagnier JJ, Oltean H, van Tulder MW, Berman BM, Bombardier C, Robbins CB. Herbal medicine for low back pain: a cochrane review. *Spine (Phila Pa 1976)*. 2016; 41(2): 116-133.
[25] Kalim MD, Bhattacharyya D, Banerjee A, Chattopadhyay S. Oxidative DNA damage preventive activity and antioxidant potential of plants used in Unani system of medicine. *BMC Complement Altern Med*. 2010; 10: 1-11.
[26] Kim MG, Lee SE, Yang JY, Lee HS. Antimicrobial potentials of active component isolated from *Citrullus colocynthis* fruits and structure-activity relationships of its analogues against foodborne bacteria. *J Sci Food Agric.* 2014; 94(12): 2529-2533.
[27] Gurudeeban S, Satyavani K, Ramanathan T. Bitter apple (*Citrullus colocynthis*): An overview of chemical composition and biomedical potentials. *Asian J Plant Sci*. 2010; 9(7): 394-401.
[28] Huseini HF, Darvishzadeh F, Heshmat R, Jafariazar Z, Raza M, Larijani B. The clinical investigation of *Citrullus colocynthis* (L.) schrad fruit in treatment of type II diabetic patients: a randomized, double blind, placebo-controlled clinical trial. *Phytother Res*. 2009; 23(8): 1186-1189.
[29] Shi C, Karim S, Wang C, Zhao M, Murtaza G. A review on antidiabetic activity of *Citrullus colocynthis* Schrad. *Acta Pol Pharm*. 2014; 71(3): 363-367.
[30] Benariba N, Djaziri R, Hupkens E, Louchami K, Malaisse WJ, Sener A. Insulinotropic action of *Citrullus colocynthis* seed extracts in rat pancreatic islets. *Mol Med Rep*. 2013; 7(1): 233-236.
[31] Mehrzadi S, Shojaii A, Pur SA, Motevalian M. Anticonvulsant activity of hydroalcoholic extract of *Citrullus colocynthis* fruit: involvement of benzodiazepine and opioid receptors. *J Evid Based Complement Altern Med.* 2016; 21(4): 31-35.
[32] Vakiloddin S, Fuloria N, Fuloria S, Dhanaraj SA, Balaji K, Karupiah S. Evidences of hepatoprotective and antioxidant effect of *Citrullus colocynthis* fruits in paracetamol induced hepatotoxicity. *Pak J Pharm Sci*. 2015; 28(3): 951-957.
[33] Tannin-Spitz T, Grossman S, Dovrat S, Gottlieb HE, Bergman M. Growth inhibitory activity of cucurbitacin glucosides isolated from *Citrullus colocynthis* on human breast cancer cells. *Biochem Pharmacol*. 2007; 73(1): 56-67.
[34] Dhanotia R, Chauhan NS, Saraf DK, Dixit VK. Effect of *Citrullus colocynthis* Schrad fruits on testosterone-induced alopecia. *Nat Prod Res*. 2011; 25(15): 1432-1443.
[35] Rajamanickam E, Gurudeeban S, Ramanathan T, Satyavani K. Evaluation of anti-inflammatory activity of *Citrullus colocynthis*. *Int J Curr Res*. 2010; 2: 67-69.
[36] Ramanathan T, Gurudeeban S, Satyavani K.

Local anesthetic effect of *Citrullus colocynthis* on rana hexadactyla. *Res J Med Plant*. 2011; 5(3): 338-342.

[37] Heydari M, Homayouni K, Hashempur MH, Shams M. Topical *Citrullus colocynthis* (bitter apple) extract oil in painful diabetic neuropathy: A double-blind randomized placebo-controlled clinical trial. *J Diabetes*. 2016; 8(2): 246-252.

Abbreviations

DALY: disability-adjusted life-years; GBD: global burden of diseases; HALE: Injuries and healthy life expectancy