



Leech Therapy in the Osteoarthritis of Knee Joint

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ABSTRACT

Irsal-e-alaq, (leeching/ leech therapy) has been in use since antiquity. There is a long list of diseases for which its application can be traced in Unani system of medicine. Osteoarthritis is one of them. In this study we have evaluated the effect of leeching in patients of osteoarthritis of knee. This was a single blind randomised controlled clinical trial, done on 60 patients. All the patients were allocated into two groups, comprising of 30 patients in the test group and 30 patients in the control group. Leech therapy was given to the patients of test group, once weekly for the duration of four weeks. Patients of the control group were advised to apply diclofenac gel topically, twice daily on the affected area for the same duration. Encouraging results were obtained at the end of the study. All the data were statistically evaluated.

KEYWORDS : Irsal-e-alaq, Leeching, Osteoarthritis

Introduction

Osteoarthritis is a degenerative joint disease characterized by joint pain, tenderness, stiffness, locking of joints, or sometimes there may be effusion. It may be hereditary, developmental, metabolic and/or mechanical^[1]. Renowned ancient unani physicians like Zakaria Razi, Ibn-Sina, Sharfuddin Ismail Jurjani had described osteoarthritis and its management in detail in their books^[2,3,4,5]. During the reign of King Aurangzeb (1658-1707), Hakeem Mir Mehdi, Hakeem Alavi Khan, Hakeem Mohammad Akbar Arzani, Hakeem Mohammad Azam Khan (a renowned scholar and physician of post Mughal period) also described osteoarthritis in their famous books^[6]. In Unani system of medicine osteoarthritis is classified on the basis of various factors like Mizaj or temperament Barid (cold), Ratab (wet), Yabis (dry), Har (hot), Har Yabis (hot and dry), Har Ratab (hot and wet), Barid yabis (cold and dry), Barid Ratab (cold and wet)), presence or absence of morbid humors (waja-ul-mafasil sada or maddi), involvement of number of humor (mufrad/single or murakkab/multiple), involvement of material or madda (Damvi/sanguineous, Balghami/phlegmatic, Saudavi/melan-cholic, Safravi/bilious, Reehi/pneumatic, Ufooni/infectious), on the basis of severity and duration of the disease (acute or chronic)^[7]. Zakaria Razi described the vitiated Phlegm as the most common cause of disease, but sometimes may be blood, bile or rarely sauda is the cause whereas according to Ibn Sin some factors may directly (mal-temperament and morbid humors) or indirectly responsible for the diseases^[3,8,9]. Incidence of osteoarthritis of knee joint is 30 cases per 10,000 population^[10] and is common in the age group of 40-50 years of age^[11] and is more common in females^[12] common in temperate climate^[13] increased incidence in urban communities^[14]. There are few risks factors which can predispose osteoarthritis. The Most Common are being female which is obese, certain sports and previous joint trauma etc^[15]. Osteoarthritis can affect any joint but mostly the weight bearing joints are involved^[16].

In modern system of medicine osteoarthritis is treated with Non Pharmacological management (NPM) with pharmacotherapy as well. Non Pharmacological management includes patients education,^[17] physical exercises,^[18] weight management,^[19] sometimes assistive devices^[20] and dietary supplements like glucosamine sulphate and chondroitin sulphate also be used,^[21] analgesics like acetaminophen,^[22] NSAID'S opioids, Intra articular corticosteroids injection^[23] and local analgesics capsaicin^[24] are widely used as Pharmacotherapy worldwide for the treatment of osteoarthritis of knee joint.

In unani medicine osteoarthritis of knee joint is treated with Asbab-e-sitta-e-zarooriya. According to unani system osteoarthritis is due to accumulation of morbid matter within the body, which are to be removed by various drugs like coctives (munzijat), laxatives and purgatives (mullaiyanat and mushilat), Diuretics (mundir-e-bol) and resolvents (muhallilat), Analgesics (musakkinat-e-alam) loosening

agents (murakhiyat), nervine tonics (muqavvi-e-asab) immunomodulatory and antioxidants and also by diet apart from above mentioned treatment^[25,26,27].

Certain regimental therapies play an important role in the management of osteoarthritis. One of them is leeching (Irsal-e-Alaq/hirudo therapy/leech therapy). Leeching is a method of bloodletting which involves the withdrawal of blood in a considerable amount from the body with the help of leeches.^[28] Medicinal leeches were widely used in ancient times^[29,30]. The concept of leech therapy was first introduced by famous unani physician "Hippocrates" (460-370 B.C) "Father of Medicine"^[31]. Avicenna (980-1037 A.D) also described the procedure of leech therapy and he believed that leeches draw blood from deeper sources than wet cupping^[32,33,34]. Leeching is also mentioned in ayurvedic medicine and is described in Sushruta Samhita as Jalaukavacharan (jalauka-Leeches, avacharan-application)^[35]. In 20th century, leeches were used in reconstructive surgeries like breast reconstruction etc^[36]. In 1983, Handerson et al used leeches in the operative treatment of scalp avulsion case^[37]. Leeches are also used on those areas of the body where other processes of blood-letting like Venesection and Cupping are not possible^[38,39]. The leech therapy practiced successfully upto 16th century after that some scientific evidences discredited it^[40]. According to Unani system of medicine, leeches work on the principle of evacuation and diversion of morbid humors (Tanqiyae mawad and Imalae mawad) and it is widely used to treat number of diseases and effectiveness of leech therapy attributed to sedative and anti-inflammatory actions of saliva^[29,38,41]. The leech saliva contains about 100 pharmacologically active biological substances. These includes anticoagulants like hirudin, calin, inhibitors of kallikrein, collagenase. It also contains some anaesthetic and analgesic compounds^[38,29]. Leech therapy is used to treat chronic skin diseases, eye diseases, musculoskeletal diseases, gynaecological and ENT disorders, thrombo-embolic diseases etc. The commonest indications in unani system of medicine are varicose veins, painful calf muscles, blepharitis, mania, non-healing ulcers, infected wound, sinusitis, pharyngitis, piles, fistula in ano, elephantiasis, ringworm, chloasma, warts, eczema, psoriasis, vitiligo, osteoarthritis, hypertension, snakebite etc^[29,41,42,43,44]. Nowadays, it is widely used in plastic surgery coronary artery thrombosis, ischaemic heart disease and other reconstructive surgeries worldwide^[45]. Leech therapy is contraindicated in certain medical conditions like haemorrhagic diseases, absolute haemophilia, pregnancy, severe anaemia, hypotension, allergy, to leech, high temperature, immuno-compromised patients, severely ill and bedridden patients and also in fearful individuals^[41]. Leeches are not applied on abdomen especially around liver, spleen, stomach, intestine and buttocks^[41,46]. There is a risk of certain adverse effects of leech application like pain, local itching, hypotension, vasovagal attack, anaemia, infection, allergy, sepsis, transmission of infectious diseases, scarring and slight fever^[34,47,48]. Leech therapy reduces pain, stiffness and joint

dysfunction in the patients with osteoarthritis of knee joint due to its anaesthetic, anti-inflammatory and immune-stimulant action [49,50,51]. The Present study is designed to assess the efficacy of leech therapy in the management of osteoarthritis of knee joint.

Material and Methods

This study was an experimental randomised controlled clinical trial conducted in the department of Surgery in collaboration with department of Regimental therapy, AK Tibbiya College, AMU, Aligarh. 60 patients diagnosed with osteoarthritis of knee joint were included in the study. Patients randomly divided into two groups as test group (30 patients) and control group (30 patients). Written and well informed consent was taken before participation in the study. The protocol was approved by institutional ethical committee. After detailed history every patient was examined clinically and their haematological and biochemical (complete Haemogram with ESR, BT, CT, RA factor, CRP, uric acid) and radiological (X-ray of the affected knee joint) investigations were carried out.

2.1 Inclusion criteria

Age between 40-80 years of age of either sex.

Clinical and/or radiological evidence of osteoarthritis.

Exclusion criteria

Patient below the age of 40 yrs and above the age of 60 yrs, Pregnancy, Lactation, Diabetes Mellitus, Anaemia (Hb% <10 gm%), Liver disease, Renal failure, Ischaemic Heart diseases, Other types of Arthritis.

The patients in the test group underwent 4 sittings of leech therapy once in a week period while in control group diclofenac gel was applied locally twice daily on the affected joint for a period of 28 days. Patients were assessed for a period of 6 weeks (0day, 7th day, 14th day, 28th day, 42nd day). The duration of trial was 42 days and the assessment of subjective and objective (ESR, X-ray) parameters were done fortnightly. The assessment was done on the basis of VAS Score [52,53]. The pre-treatment and post treatment data were tabulated and statistically analysed by applying unpaired 't' test.

Result and Observation

Clinical evaluation was done on the basis of subjective and objective parameters. The age of the patients ranged from 40 to 79 yrs of age in both the groups with mean age of 58.17 ± 9.99 years (test group) and 60.17 ± 10.40 years (controls) (Table 1). Maximum number of patient were in the age group of 50-59 years of age.

Table 1- According to Age

Age (yrs)	Test Group		Control	
	No.	%	No.	%
40-49	6	20.0	5	16.7
50-59	12	40.0	10	33.3
60-69	7	23.3	8	26.7
70-79	5	16.7	7	23.3
Total	30	100	30	100

Out of 60 patients (30 in each group), 19(63.3%) were females and 11(36.7%) were males in test group (male:female ratio 1:1.7) while in control group, there were 22 (73.3%) females and only 8 (26.7%) were males (male:female ratio1:2.7) . (Table 2)

Table 2- According to Gender

Gender	Test Group		Control	
	No.	%	No.	%
Male	11	36.7	8	26.7
Female	19	63.3	22	73.3
Total	30	100	30	100

In test group, there were 76.7% (23 patients) non-vegetarians and 23.3% were vegetarians on the other hand, 83.3% (25 patients) were non-vegetarians and 16.7 (5 patients)were vegetarians in control group (Table 3). Obesity and BMI are particularly associated with knee osteoarthritis.

Table 3- According to Dietary habit

Diet	Test Group		Control	
	No.	%	No.	%
Vegetarian	7	23.3	5	16.7
Non-Vegetarian	23	76.7	25	83.3
Total	30	100	30	100

According to the temperament, osteoarthritis is predominant in Balghami temperament patients followed by Saudavi and Safravi temperament and least number of patients belong to Damvi temperament in both the groups (test as well as control group) (Table 4).

Table 4- According to Temperament

Temperament	Test Group		Control	
	No.	%	No.	%
Balghami	21	70.0	18	60.0
Safravi	3	10.0	5	16.7
Saudavi	5	16.7	5	16.7
Damvi	1	3.3	2	6.67
Total	30	100	30	100

Effect on pain was also observed in test group and controls and there was statistically significant difference between the two groups (t=3.2, p<0.001).

Table 5-Effect on VAS

Test group

Score	Visual Analogue Score (VAS)							
	BT		14 th day		28 th day		AT	
	No	%	No	%	NO	%	No	%
0-1 (no pain)	0	0.0	3	10.0	8	26.7	17	56.7
2-3 (mild)	5	16.7	10	33.4	11	36.7	7	23.3
4-5 (uncomfortable)	19	63.3	13	43.3	10	33.3	6	20.0
6-7 (distressing)	4	13.3	4	13.3	1	3.3	0	0.0
8-9 (intense)	2	6.7	0	0.0	0	0.0	0	0.0
10 (worst possible)	0	0.0	0	0.0	0	0.0	0	0.0
Total	30	100	30	100	30	100	30	100

Control group

Score	Visual Analogue Score (VAS)							
	BT		14 th day		28 th day		AT	
	No	%	No	%	NO	%	No	%
0-1 (no pain)	0	0.0	1	3.3	5	16.7	5	16.7
2-3 (mild)	4	13.3	12	40.0	11	36.6	13	43.3
4-5 (uncomfortable)	17	56.7	10	33.3	11	36.6	8	26.7
6-7 (distressing)	5	16.7	7	23.3	3	10.0	4	13.3
8-9 (intense)	4	13.3	0	0.0	0	0.0	0	0.0
10 (worst possible)	0	0.0	0	0.0	0	0.0	0	0.0
Total	30	100	30	100	30	100	30	100

Mild degree of Joint stiffness of the involved joint was present in maximum number of patients in both the groups (17 out of 30 in test group and 14 out of 30 in control group) but there is no significant difference between the test and control group(t= 0.59).

Table 6- effect on Joint Stiffness

Test group

Score	Joint Stiffness							
	BT		14 th day		28 th day		AT	
	No	%	No	%	NO	%	No	%
0-nil	1	3.3	4	13.3	9	30.0	16	53.3
1-mild	14	46.7	13	43.3	15	50.0	11	36.7
2-moderate	11	36.7	11	36.7	6	20.0	3	10.0

3-severe	4	13.3	2	6.7	0	0.0	0	0.0
Total	30	100	30	100	30	100	30	100

Control group

Score	Joint Stiffness							
	BT		14 th day		28 th day		AT	
	No	%	No	%	NO	%	No	%
0-nil	0	0.0	0	0.0	4	13.3	10	33.3
1-mild	17	56.7	21	70.0	20	66.7	18	60.0
2-moderate	9	30.0	8	26.7	6	20.0	2	6.67
3-severe	4	13.3	1	3.3	0	0.0	0	0.0
Total	30	100	30	100	30	100	30	100

Leech therapy was found effective in Crepitus of the involved joint, it decreases significantly and the difference was statistically significant (t=2.0, p<0.05).

Table 7- Effect on Crepitus Test group

Score	Crepitus							
	BT		14 th day		28 th day		AT	
	No	%	No	%	NO	%	No	%
0-Absence	0	0.0	0	0.0	1	3.3	2	6.7
1-mild	14	46.7	16	53.4	17	56.7	18	60.0
2-moderate	11	36.6	10	33.3	8	26.7	7	23.3
3-severe	5	16.7	4	13.3	4	13.3	3	10.0
Total	30	100	30	100	30	100	30	100

Control group

Score	Crepitus							
	BT		14 th day		28 th day		AT	
	No	%	No	%	NO	%	No	%
0-Absence	0	0.0	0	0.0	0	0.0	0	0.0
1-mild	10	33.3	11	36.7	11	36.7	13	43.3
2-moderate	13	43.3	12	40	13	43.3	10	33.3
3-severe	7	23.3	7	23.3	6	20	7	23.3
Total	30	100	30	100	30	100	30	100

Discussion

The incidence of osteoarthritis increases with age and mostly found in 5th and 6th decade of life^[54]. In allopathic medicine, NSAID'S are the only treatment and it has enormous side effects including gastric toxicity whereas in Unani system of medicine, different non-medicinal or regimental treatment are available to treat osteoarthritis like cupping, leeching, venesection etc. Leeching is one of the effective treatments for osteoarthritis which have been used since decades, but it is not proven scientifically. This clinical study was conducted to evaluate the therapeutic potential of leeching in the management of osteoarthritis of knee joint on unani and modern scientific parameters.

In the present study, the age of the patients ranged from 40-79 years of age (mean age) in both the groups. Michalsen et al showed that the mean age of the patients is 69 ± 9 years of age^[54]. Zaidi et al included the patients between the age of 40-70 years of age. The mean age of the patients in test group was 59.90 ± 2.7 years and 57.85 ± 7.49 years in controls^[46]. A review done by Bindu Nair and Regina Taylor in 2010 in musculoskeletal diseases including osteoarthritis knee quoted that 1/5 (one fifth) of the patient were beyond the age of 65 years^[55]. In 2003 Michalsen and Klotz et al conducted a study on 51 patients with the mean age of the patients was 62.5 ± 10.2 years in test group and 65.5 ± 6.7 years in control group^[51].

Out of 60 patients (30 test group and 30 controls) there were 11 (36.7%) males and 19 (63.3%) females in test group while in control group there were only 8 (26.7%) males and 22 females (73.3%). Other subsequent study showed 40% (16 out of 40) males and 60% (24 out

of 40) females with 1:1.5 male: female ratio^[56]. Another study done by Michalsen et al in 2003 shows 35.3% males and 64.7% females in their study^[51].

There were 7 (23.3%) vegetarians and 23 (76.7%) non-vegetarians included in the test group and 5 (16.7%) vegetarians and 25 (83.3%) non-vegetarians in the control group. There is a common belief that the diet and life style can influence the appearance of arthritis. Susceptibility and predisposition to osteoarthritis depends on association of various risk factors. Obesity, female gender and increased body mass index are particularly associated with knee osteoarthritis, sometimes previous knee injury may also predispose to osteoarthritis^[57,58]. A recent study was conducted to determine the association of osteoarthritis with dietary factors such as quantity and quality of nutrient intake, shows nutritional imbalance along with endocrine abnormalities may be involved in the pathogenesis of osteoarthritis^[59]. Recently in 2015 a study was conducted to study the relation of non-vegetarian foods in the causation of osteoarthritis and they quoted that in 76.7% patients having osteoarthritis are non-vegetarians^[60] which is in conformity with Majusi^[61] Avicenna,^[58] Razi^[3] who advised the restriction of non-vegetarian diets in Waja-ul-Mafasil, as these are not easily digestible and leads to weakness of Quwwat-e-Hazima (Digestive Faculty) by producing Akhlat-e-Fasida (Morbid Humours)^[62,63, 64] Along with the increase in age there is an exponential increase in the associated risk factor of obesity due to progressive sedentary behaviour, changes in life style pattern, diet routine and work environment conditions among the adult population^[65].

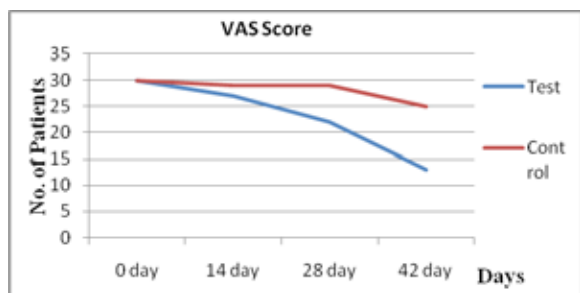
Maximum number of the patient having osteoarthritis of knee had balghami temperament in both the groups. A study done in Kashmir, India in 2013 postulated that osteoarthritis is more prevalent in balghami temperament patients^[66]. This finding supports the opinion of Avicena,^[67] Ismail Jurjani,^[68] Razi,^[45] Azam Khan^[69] as this disease is common among balghami temperament patients. Raban Tabri defined Waja-ul mafasil as the pain occurring in legs due to buroodat (coldness) and insensitivity and is balghami in temperament^[70].

In our study, there was statistically significant difference in VAS score (t=3.2, p< 0.001) and crepitus (t=2.0, p<0.05) between the test and control group but there is no significant difference in joint stiffness (t=0.59) between both the group. A study done by Michalsen and Klotz et al in 2003 to compare the effects of leech therapy and topical diclofenac gel in osteoarthritis of the knee shows statistically significant difference between the two groups (p<0.001) and the effect was maintained until 91 Days. The authors suggest re-treatment of leech therapy becomes clinically valuable in the long term management of osteoarthritis and are well tolerated and are well tolerated as well as effective. This study is concordant with our study^[51]. R.A. Moore et al quoted that topical non steroidal anti-inflammatory drugs are significantly more effective than placebo in relieving pain in acute and chronic conditions^[71]. Another study done by Zaidi et al shows significant improvement in the WOMAC pain, stiffness and function over 6 weeks period as compared to controls and they found leech therapy is safe effective and well tolerated for the symptomatic treatment for osteoarthritis of the knee^[44]. Various researchers underwent studies to demonstrate the efficacy of topical diclofenac gel(1%, 1.5%, 2%) in osteoarthritis of the knee and postulated that it is quite effective and safe as compared to oral NSAID'S in test group as compared to placebo in pain and joint stiffness^[72,73,74,75]. Michalsen A et al in 2002 conducted a study to determine the effects of leeching as an adjuvant treatment in painful osteoarthritis of the knee with a single trial of 4 leeches applied topically at painful peri-articular site of the knee and concluded that leech therapy may be an effective treatment for rapid reduction of pain associated with osteoarthritis of the knee^[54]. A meta-analysis of randomized controlled trials done to evaluate the efficacy of topical NSAID'S in the treatment of osteoarthritis shows that topical NSAID'S were superior to placebo in relieving pain and function only in first two weeks of treatment but not in the further two weeks treatment. Improvement in stiffness was seen at first week only and not in the second week^[76].

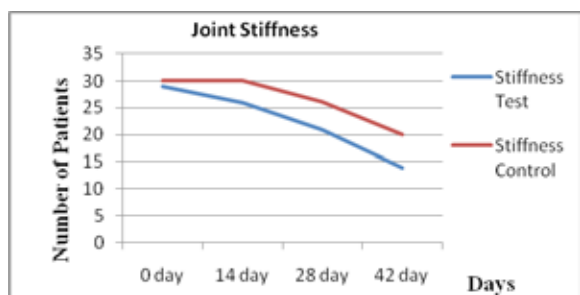
Conclusion

We conclude that leech therapy is painless, safe, effective, well tolerated and minimally invasive procedure for the treatment of osteoarthritis of the knee. The active constituents present in the leech saliva are very much beneficial and needs further study on larger sample size.

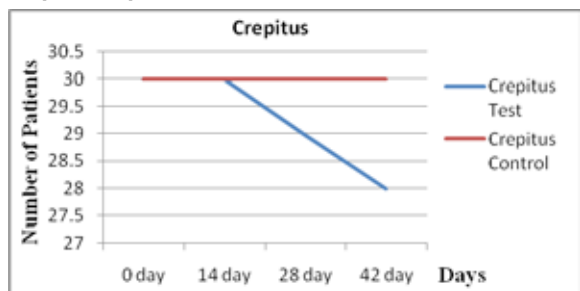
Graph of VAS Score



Graph of Joint Stiffness



Graph of Crepitus



References

- Conaghan P. Osteoarthritis - national clinical guideline for care and management in adults. (PDF). Retrieved 2008-04-29.
- Shanon Wilder. An Arthritis Timeline. <http://www.arthritis.org/resources/arthritis-to-day/2000/archives/2000-01-02-timeline.asp>.
- Zakaria Razi. Al Havi fit tib. Vol. XI, New Delhi: central council of research in unani medicine: 2004; 75-188.
- Ibn Sina. Al Qanoon fit tib. Vol I, II, III. Bairoot; Dar Ahyaee Turatil Arabi; 2002; 301, 54, 171, 271, 749, 751, 752, 164, 187, 231, 305, 344, 360, 368, 370.
- Ismail Jurjani. Tarjuma Zakheera-e-Khawarizam Shahi. Vol. II. Lucknow: Munshi Nawal Kishore; 1878: 1448-451.
- Altaf Ahmad Azami. History of Unani Medicine in India. New Delhi: Jamia Hamdard; 2004: 1-253.
- Kabeeruddin. M Moalijat Sharhe Asbab. Vol IIIrd. Hyderabad. Hikma Book Depot 1916: 213-230.
- Akbar Arzani. Meezan-ut-Tib. New Delhi; Idara-e-kitab-us-shifa, Daryaganj. 2005: 224-226.
- Ibn Sina. Al-Qanoon (urdu translation by GH Kintoori). Vol. 3rdLucknow: Munshi Naval Kishore; 1930: 293-305.
- Dennis L et al. Harrison's principles of internal medicine. Vol II. New York: Mc Graw-Hill, Medical publishing division. Pp 1968-977.
- Cremer P, Hunt M, Dippe P. Pain mechanism in osteoarthritis of the knee. Effect of intra-articular anaesthetic. J. Rheumatology. 1996; 23(6): 1031-1036.
- Kumar and Clark. Clinical medicine. 5th ed. London: WB, Saunders; 2000. pp 37-47.
- Birendra Prasad. Principles and Practice of medicine. A textbook for students and practitioners. New Delhi. Jaypee Brothers, Medical publishers (pvt) ltd. 1997; 594-599.
- John. Axford. Medicine. London: Black well science, 25, John Street; 1996. Pp 3.18-3.22.
- <http://www.zoomout-ph.com/2012/02/osteoarthritis-concept-map.html>.
- Water on the Knee. Mayo clinic.com.
- Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, et al. Guidelines for the medical management of osteoarthritis. Part II, osteoarthritis of the knee.

- American college of rheumatology. Arthritis Rheum. 1995; 38: 1541-1546.
- Kovar PA, Allegrante JP, Mackenzie CR, Peterson MG, Gutin B, Charlson ME. Supervised fitness walking in patients with osteoarthritis of the knee - randomised controlled trial. Ann. Intern Med. 1992; 116: 529-534.
- Blount WP. Don't throw away the cane. J. Bone Joint Surg. [AM]. 1956; 38: 695-8.
- Minor MA, Hewett JE, Weibel RR, Anderson SK, Kay DR. Efficacy of physical conditioning exercise in patients with rheumatoid arthritis and osteoarthritis. Arthritis Rheum. 1989; 32: 1396-405.
- Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham study. Ann. Intern Med. 1992; 116: 535-9.
- Vasan N, Tao L, Vikas B. First aid for the USMLE step 1, 2010. Mc-Graw Hill Medical. 2010; pp-378. ISBN 0-07-163340-5.
- Friedman DM, Moore ME. The efficacy of intra articular steroids in osteoarthritis: a double blind study. J. Rheumatol. 1980; 7: 850-6.
- Altman RD, Aeun A, Holmburg CE, Pfeifer LM, Sack M, Young GT. Capsaicin cream 0.025% as monotherapy for osteoarthritis: a double blind study. Semin. Arthritis Rheum. 1994; 23 (3): 525-33.
- Sheel Nidhi. Nourishing and Healing powers of garden cress (Lepidium Sativum Linn.)- A review. Indian journal of Natural products and resources. 2011; 2: 292-297.
- A. Al-Yahya. Pharmacological and safety evaluation studies on Lepidium Sativum L. seeds, medicinal, aromatic and poisonous plants research centre, college of pharmacy, King Saud University, Riyadh, Saudia Arabia Phytomedicine. Gustav Fischer Verlag, Stuttgart jena, New York. 1994; 1: 155-159.
- Rawal DN. Clinical trials of Lepidium Sativum Linn. (chandrashura) in the management of Sandhivata (osteoarthritis). 2009. AYU- 30(2): 152-157.
- Sina I. Al Qanoon fit tib. IInded. Pasha Mazhar H, translator Karachi, Pakistan. Inter services Press; 1998: 408-409.
- Adams SL. The medicinal leech. A page from the Annelids of internal medicine. Ann. Intern. Med. 1998; 109: 399-405.(PMID-3044211)
- Fields WS. The history of leeching and hirudin. Haemostasis. 1991; 21(1); 3-10. PMID-1894194)
- Price RA. Treatise on the utility of Sangui-Suction or leech bleeding. London: Simpkin and Marshall; 1822. Pp. 3-4.
- Haycox CL, et al. Indications and complications of medicinal leech therapy. American academy of dermatology. 1995; 12(3): 165-72. [PubMed]
- Godfrey K. Uses of leeches and leech saliva in clinical practice. Nursing time. 1997; 62-63.
- Gruner OCA. Treatise on the Canon of medicine of Avicenna- incorporating a translation of the first book. London; Luzac & Co; 1930. Pp. 513-4.
- Verma DK, Chaubey PK, Singh AK, Singh OP. A critical review on historical aspect of Jalaukavacharan (hirudotherapy). IJRAP [internet] 2012; 3(1): Pp 3.
- Giacometti. Leeching in the twentieth century. The American journal of cardiology. 1987; 60: 1130.
- Handerson HP, et al. Avulsion of the scalp treated by microvascular repair- the use of leeches for post operative decongestion. Br. J. Plast. Surg. 1983; 36: 236-37.
- Majusi AIA. In: Kamilus Sana: Kantoori G.H. New Delhi: Idara kitabush Shifa; 1889. 2; 503-504.
- Al-Maseehi I Q. Kitabul umda, urdu translation by CCRUM, Ministry of health and family welfare. New Delhi. 1986; 1: 200-201.
- Robert NM, David M, David AB. The leech and the physician: biology, etymology and medicinal practice with Hirudinea medicinalis. W. J. Surg. 2000; 24: 878-83.
- Tabri R. In Firdaus-ul-hikmat. Shah Mohammad Adil. Deoband. Faisal publications.2002; 306.
- Vohra SB, Khan SY. Animal origin drugs used in unani medicine. New Delhi. Vikas publishing house; 1979: Pp. 6, 52, 58, 64, 96, 121.
- Razi AMBZ. Kitab al Mansoori (urdu translation by CCRUM), New Delhi. Ministry of health and family welfare, government of India; 2002; 284: 391-94.
- Abbas SM, Jamil SS, Sultana A, et al. Safety and efficacy of leeching therapy for osteoarthritis using Indian medicinal leech. Indian J. traditional Knowledge. 2009; 8(3): 437-442.
- Kreamer BA, Korber KE, Aquino TI, Engleman A. Use of leeches in plastic and reconstructive surgery - a review. J. Reconst. Microsurg. 1988: 381-386.
- Hubal I. Kitabul Mukhtarar Fil Tibb, (Urdu translation by CCRUM) 1, 2, 3, 4. New Delhi: Ministry of Health & Family Welfare, Govt. of India; 2005. p. 81, 96, 79-91, 205.
- Anonymous; The wealth of India. VI: L-M. New Delhi: Council of Scientific & Industrial Research (CSIR); 2003. pp. 57-59.
- Orevi M, Rigbi M, Matzner Y, Elder A. A Potent inhibitor of platelet activity factor from the saliva of the leech hirudo medicinalis. Prostaglandins. 1992; 43: 483-489.
- Sawyer RT. Leech biology and behavior. New York: Oxford University press; 1986
- Weinfeld AB, Yuksel E, Boutros S, Gura DH, Friedman JD. Clinical and Scientific considerations in leech therapy for the management of acute venous congestion - a review. Ann. Plast. Surg. 2000; 45: 207-212.
- Michalsen A, Klotz Stefanie, Lütke Rainer, et al. Effectiveness of Leech Therapy in Osteoarthritis of the Knee: A Randomized, Controlled Trial. Ann Intern Med. 2003; 139: 724-730.

52. Mohsin M. Effects of glucosamine sulphate on primary knee osteoarthritis. *Al Ameen J. Med. Sci.* 2008; 1: 42-9.
53. Lund H, Weile U, Christensen R, Rostok B, Downey A, Bartels EM, et al. A randomised controlled trial on Aquatic and land based exercise in patients with knee osteoarthritis. *J. Rehab. Med.* 2008; 40: 137-44.
54. Michalsen A, Moebus S, Spahn G, Esch T, Langhorst J, Dobos GJ. Leech therapy for symptomatic treatment of knee osteoarthritis: results and implications of a pilot study. *Alter. Ther. Health Med.* 2002; 8 (5): 84-88.
55. Bindu Nair and Regina Taylor. A review of topical diclofenac use in musculoskeletal disease. *Pharmaceuticals (Basel).* 2010; 3(6): 1892-1908.
56. Muller IW. *Handbuch der Blutegeltherapie: Theorie and Praxis.* Stuttgart: haug; 2000.
57. Edwards CRW, Bouchier IAD, Haslet C, Chilvers ER. *Davidson's: Principles and Practice of Medicine.* 17th edition (international students edition). Churchill Livingstone, medical division of Pearson Professional limited. New York. 1996 (reprinted); 877.
58. Silverwood V, Blagojevic-Buckhall M, Jinks C, Jordan JL, Protheroe J, Jordan KP. Current Evidence on risk Factors for Knee osteoarthritis in older adults: a systemic review and meta analysis. *Osteoarthr. Cartil.* 2015; 23: 507-515.
59. Sanghi D, Mishra A, Sharma AC, Raj S, Mishra R, Kumari R, Natu SM, Agarwal SM, Srivastava R. Elucidation of dietary risk factors in osteoarthritis knee- a case control study. *J. Am. Coll. Nutr.* 2015; 34: 15-20.
60. Mohammad Khalid. Clinical evaluation of Majoon Yahya bin Khalid and local application of roghan darchini in the management of 1^o knee osteoarthritis. *J. Biol. Sci. Opin.* 2015; 3(6): 271-77.
61. Majusi IA. *Kamilus Sana (urdu translation by Kantoori GH).* 1st edition, Idara Kitabus shifa, New Delhi. 2010.
62. Shadab M, Zulkifle M, Ansari AH, Itrat M. Prevalence of knee osteoarthritis in patients visiting NIUM hospital, Bangalore. *IJHM.* 2014; 2(2): 61-64.
63. Hawamdeh ZM, Al-Ajlouni JM. The Clinical pattern of knee osteoarthritis in Jordan- A hospital based study. *Int. J. Med. Sci.* 2013; 10(6): 790-795.
64. Nayab M, Anwar M, Quanri MA. Clinical study on waja-ul-mafasil and evaluation of efficacy of Hijamah bila shurt in the treatment. *IJTK.* 2011; 10(4): 697-701.
65. Esser S, Bailey A. Effect of exercise and physical activity on knee osteoarthritis. *Curr. Pain Headache rep.* 2011; 15: 423-30.
66. Dar AK, Lone AH. Prevalence of Musculoskeletal diseases in patients visiting government unani hospital and ayush centres in Kashmir, India- A preliminary study. *Int. J. Res. Ayurveda pharm.* 2013; 4(4): 475-478.
67. Ibn Sina. *Al Qanoon Fit Tib (urdu translation by Kantoori GH).* Vol. III, Idara Kitabus shifa, New Delhi. 2007; Pp. 119-125.
68. Jurjani I. *Zakheera Khawarzam Shahi (urdu translation by Khan HH).* Vol. 2nd, 3rd, part 8. Munshi naval kishore, Lucknow. 1996; Pp. 225-26, 637-51.
69. Khan MA. *Akseer Azam.* Vol. 4th Munshi naval kishore, Lucknow. 1998; 13-36.
70. Tabri R. *Wajaul Warik, Wajaul Mafasil, Irqun Nisa, Niqris.* In *Firdaus-al-hikmat.* 1st edition. Faisal publications. New Delhi. 2002; 291.
71. Moore RA, Tramer MR, Caroll D, Wiffen PJ, McQuay HJ. Quantitative systemic review of topically applied non-steroidal anti-inflammatory drugs. *BMJ.* 1998; 316: 333-338.
72. Bookman, AAM, Williams, KSA, Shainhouse JZ. Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: A randomized controlled trial. *CMAJ* 2004; 171 (4): 333-338.
73. Roth, SH, Shainhouse JZ. Efficacy and safety of a topical diclofenac solution (pennsaid) in the treatment of primary osteoarthritis of the knee: A randomized, double-blind, vehicle-controlled clinical trial. *Arch. Intern. Med.* 2004; 164 (18): 2017-2023.
74. Simon, LS, Grierson, LM, Naseer Z, Bookman AA, Zev Shainhouse J. Efficacy and safety of topical diclofenac containing dimethyl sulfoxide (DMSO) compared with those of topical placebo, DMSO vehicle and oral diclofenac for knee osteoarthritis. *Pain* 2009; 143 (3): 238-245.
75. Tugwell PS, Wells GA, Shainhouse JZ. Equivalence study of a topical diclofenac solution (pennsaid) compared with oral diclofenac in symptomatic treatment of osteoarthritis of the knee: A randomized controlled trial. *J. Rheumatol.* 2004; 31: 2002-2012.
76. Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. *BMJ.* 2004; 329(7461): 324.