REVIEW

Gout Remedies in Traditional Iranian Medicine (TIM)

Abstract

Practice and study of medicine in Iran has a long and prolific history. Iran has all characteristics of an indigenous culture which has so far discovered numerous natural products. Unfortunately, scant research has been conducted on this system of medicine and ethnopharmacology of Iran. Gout is a historical disease that is still widespread all around the world. As numerous remedies used to be administered for treating gout in TIM, we decided to investigate drugs used to target gout. To accomplish this, five of most important references of TIM form the 9th to the 18th century were investigated for gout remedies. For all herbal remedies, an extensive search of the scientific data banks, Medline and Scopus, was done to find recent possible results concerning the xanthine oxidase inhibitory, anti-inflammatory, and analgesic activities. One hundred and nine plant species, 31 animals, 14 minerals, and one mushroom were identified. Fourteen, twenty eight and three plant species have shown *in vitro* xanthine oxidase inhibitory, anti inflammatory and analgesic activities, respectively; also nine, forty and twenty two *in vivo* activities and two, seventeen and eight human studies were carried out for these three properties. Fifty-four drugs were cited in at least three references. TIM has the potential to be a very rewarding source of medical and medicinal knowledge. Then, a special focus should be put on drugs as well as the therapeutic method targeting the gout treatment. Owing to the limited attention so far paid to treating gout in TIM, it seems pertinent to conduct a systematic research on remedies which were used in TIM..

Key words: Analgesic; Anti-inflammatory; Gout; Hyperuricemia; Traditional Iranian Medicine; Xanthine oxidase inhibitory

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Introduction

Gout is a metabolic disease that most often affects middle-aged to elderly men. It is typically associated with an increased uric acid pool, hyperuricemia, episodic acute and chronic arthritis, and deposition of monosodium urate crystals in connective tissue tophi and kidneys.[1] The incidence of gout has increased significantly in recent years. Several factors, such as dietary excess, trauma, surgery, excessive ethanol ingestion, adrenocorticotropic hormone and glucocorticoid withdrawal, hypouricemic therapy, and serious medical illnesses (i.e., myocardial infarction and stroke), may lead to acute gouty arthritis. Premenopausal gout is a rare occurrence, and most women with gouty arthritis are postmenopausal and elderly.[2] The main risk factors for gout include family history, male sex, high red meat and alcohol consumption, increased longevity, metabolic syndrome, use of diuretics and end-stage renal disease.[3, 4]

Gout is a painful and debilitating condition that develops in some people who have chronically high blood levels of urate (commonly referred to as uric acid). Acute arthritis is the most frequent early clinical manifestation of gout. The metatarsophalangeal joint of the first toe is often involved, but tarsal joints, ankles, and knees are also commonly affected in elderly patients. In addition, finger joints may also be inflamed. Inflamed Heberden's or Bouchard's nodes may also be an initial clinical manifestation of gouty arthritis. The first episode of acute gouty arthritis frequently begins with dramatic joint pain and swelling, and joints rapidly become warm, red, and tender.[5]

The goal of treatment for flares of gouty arthritis is to reduce pain and inflammation quickly and safely. Anti-inflammatory medications are the best treatment for acute gout attacks, and it is best to begin treatment early in the course of an attack. Non-steroidal anti-inflammatory drugs and colchicine remain the most widely recommended drugs to treat acute attacks. Oral corticosteroids, however, could be an alternative to these drugs. Hypouricemic agents reduce uric acid concentrations by inhibiting uric acid production, inhibiting xanthine oxidase enzyme activity (allopurinol) or enhancing uric acid excretion (probenecid, benzbromarone.[6]

Besides appropriate treatment, some simple changes in the lifestyle, such as controlling body weight, reducing the consumption of red meat and seafood, increasing liquid ingestion, limiting ethanol intake and avoiding diuretics are rec-

1- Braunwald et al., 2001.
2- Ibid
3- Arromdee et al., 2002: 2403-2406.
4- Luk et al, 2005: 435-442.
5- Braunwald et al., 2001.
6- Gruber, 2009: 111-114.

ommended.[7] Coffee may decrease the risk of gout attacks, and vitamin C (500 mg/day) also has a mild urate-lowering effect.[8]

Gout is one of the oldest diseases, and its identification goes back to more than 4,500 years in Egypt.[9, 10] There is also a description of gout in the Bible and the Talmud (*ca.* 2,000 years ago).[11- 13] Moreover, gout is also described in the Atharvaveda, which is one of the historical and main books of Ayurveda.[14] In the fifth century BC, Hippocrates referred to gout as 'the unwalkable disease". Six centuries later, Galen was the first to describe tophi as the crystallized monosodium urate deposits following longstanding hyperuricemia.[15] Razi formulated a diagnosis and provided a description of obesity gout and wrote a book about gout.[16] The Ebers Papyrus revealed the administration of colchicum for the treatment of rheumatism and swelling in 1500 BC,[17] but the first use of the drug for gouty arthritis was credited to Ibn Sina.[18] In 1776, Scheele isolated uric acid from a urinary calculus, and Wollaston, in 1797, showed that gouty tophi contained uric acid.[19] Garrod's son Archibald (1931), the author of the first clinical genetics textbook, described gout as "an inborn error of metabolism".[20]

According to TIM, gout is a joint pain disease that usually starts from toes. It may disseminate to the legs and cause inflammation and a swollen scrotum in men. Gout is caused by the accumulation of bad humors in the joints. Traditional Iranian medicine identified and enumerated the main risk factors of gout as the amount and type of food consumed, digestion, abnormal or excess rest and sleep, lack of movement and exercise, indulgence in intercourse, constipation, exercise or intercourse right after eating, and drinking wine or alcohol on an empty stomach. For women, traditional Iranian medicine suggested that gout could only occur in menopausal women. In addition, gout was determined to be hereditary, and patients with gout were told to reduce their meat intake.

Traditional Iranian medicine suggested that the medicine be taken in the morning before breakfast followed by a bath six hours later. In TIM, gout treatment strategies were designed to and reduce bad humors, causing the disease, to relieve pain and to reduce inflammation. Colchicum (*Soorenjan*) was one of the significant drugs that could improve recovery, especially if it was accompanied by pepper (*Felfel*), ginger (*Zanjebil*), and caraway (*Zireh*). Massaging with croton (Dand) or old olive (*Zeitun*) oil has also been recommended. To prevent

7- Braunwald et al., 2001.
8- Choi et al, 2007: 816-821.
9- Nuki et al, 2006.
10- Pillinger et al., 2007: 215-221.
11- Rosner, 1969: 151-152.
12- Rosner, 1977: 833.
13- Rosner, 1983: 236.
14- Routh et al, 1999: 41-47.
15- Nuki et al, 2006.
16- Ligon, 2001: 266-272.
17- Graham et al, 1953: 16-19.
18- Hartung, 1954: 190-200.
19- Klinenberg, 1969: 231-243.
20- Pillinger et al., 2007: 215-221.

gout, patients should avoid concentrated and salty meats, salty foods, excessive wine and alcohol, and overeating. Patients should also avoid doing heavy exercise and sleeping right after eating.[21- 23]

This survey was the first work of the Traditional Pharmacy Department of Shiraz Faculty of Pharmacy (as the first department of Traditional Iranian Pharmacy) on TIM books. For a number of reasons, we focused this review on remedies used for gout. Firstly because gout is a historical disease that is still widespread in the world including Iran and numerous remedies have been used to treat this disease in TIM. Moreover, it seems that identical description has been given to gout both in TIM and in modern medicine. Furthermore, the mechanisms of gout and gouty pains are almost clear, and some*in vivo* and *in vitro* test systems have been established in this field. Thus, it seems quite feasible to conduct a meaningful pharmacological study in TIM.

Methodology

We have studied print versions of five original important books of TIM: Al-Hawi by Razi (9th and 10th centuries), Al-Qanun fi al-Tibb by Ibn Sina (10th and 11th centuries), Ikhtiyarat-e-Badiyee by Zein al Din Attar Ansari Shirazi (14th century), Tohfat ol Moemenin by Mohammad Tonkaboni (17th century) and Makhzan ol Advieh by Aghili Shirazi (18th century). These are among the most important references for TIM, Traditional Iranian Pharmacy (TIP) PhD courses and natural healers in Iran.[24- 27] These books cover TIM for nearly 1,000 years and show the improvements in traditional medicine. A brief description for these pharmacopeias is noted in the main table footnote.

We have searched books for the exact terminology of gout in Persian, "نقرس"(/neghres in Persian/), and gathered recommended remedies. Remedies were categorized into herbal, animal, and mineral drugs and sorted alphabetically in three distinct tables. We have omitted the remedies not completely identifiable. As mentioned above, TIM strategies for healing gout include reducing inflammation and pain as well as eradicating bad humors (which we now know as uric acid) from the body. Unfortunately, these texts have not clearly described the mechanism of the action(s) of each drug. Therefore, for all herbal remedies, we have investigated the scientific data banks like Medline and Scopus to find Remedies used as the anti-inflammatory, analgesic drugs, and uric acid

21- Aghili Shirazi, 2007a.
22- Ibn Sina, 2005.
23- Jorjani, 2006.
24- Amin, 2007.
25- Mohagheghzadeh et al., 2006: 161–184.
26- Program Book of PhD Degree in Traditional Iranian Pharmacy, 2007.
27- Hooper, 1937.

concentration reduction activity (xanthine oxidase inhibition and uricosuric). We undertook some research into the plant names and terms like gout, uric acid, hyperuricemia, uricosuric, inflammation, xanthine oxidase inhibition, antinociceptive, and analgesic.

For drug nomenclature, we used the following books: Matching the Old Medicinal Plant Names with Scientific Terminology,[28] Dictionary of Medicinal Plants,[29] Dictionary of Iranian Plant Names,[30] Popular Medicinal Plants of Iran,[31] Pharmacographia Indica,[32] Indian Medicinal Plants,[33] Seydaneh fit Teb,[34] Al-Qanun fi al-Tibb[35] and botanical descriptions of Makhzan ol Advieh.[36]

Results and Discussion

Traditional Iranian medicine and conventional medicine share a lot of similar concepts about gout, implying that they are referring to the same disease. Both systems believe that gout is caused by the accumulation of some undesired materials in certain joints. There are also some interesting epidemiological similarities such as the observations that gout is common in elderly people and that premenopausal women are rarely affected. The hereditary nature of the disease has also been in both forms of medicine. Certain food habits that increase the risk of gout, such as high food intake and excessive consumption of alcohol and meat are common in both TIM and conventional medicine. The treatment strategies including eliminating substance(s) causing the disease, reducing inflammation and relieving pain are noticed in both types of medicine.

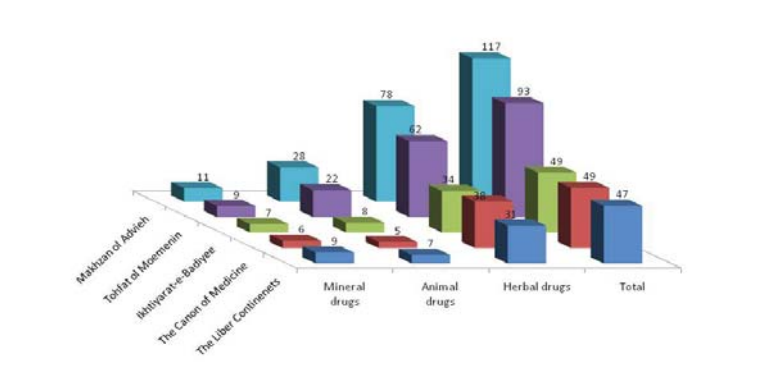

Fig.1. Number of drugs in each book.

In total, 173 drugs for the treatment of gout have been mentioned in these references. One hundred and nine plants (out of 120), 31 animals (out of 37), 14 minerals (out of 15), and

28- Ghahraman et al, 2004.
29- Soltani, 2004.
30- Mozaffarian, 2006.
31- Amin, 2005.
32- Dymook et al., 1893.
33- Khare, 2007.
34- Biruni, 2004.
35- Ibn Sina, 1998.
36- Aghili Shirazi, 2009.

one type of mushroom are identified. The abundance of drugs in each book is shown in Fig. 1, and plant species are listed in Table 1. The lists of animal and mineral drugs are also available in Tables 2 and 3, respectively (Tables are in Suplementary).

Among the plant families, Apiaceae and Brassicaceae were the most strongly represented with seven species, Asteraceae with six, and Liliaceae, Cucurbitaceae and Lamiaceae each with four species (Fig. 2). Plants from these families were also extensively used for gout treatment in other traditional medicine systems. In Europe, for example, seven species from Lamiaceae, five species from Asteraceae, and three species from Apiaceae were used for gout treatment.[37] Or, in Vietnam, 12 species from Asteraceae, five species from Apiaceae, and four species from Lamiaceae were used.[38] In China, eight species from Apiaceae, seven species from Asteraceae and Liliaceae, six species from Lamiaceae, and three species from Cucurbitaceae were used for gout treatment.[39] Finally, in North America, six species from Asteraceae[40] were used as gout remedies.

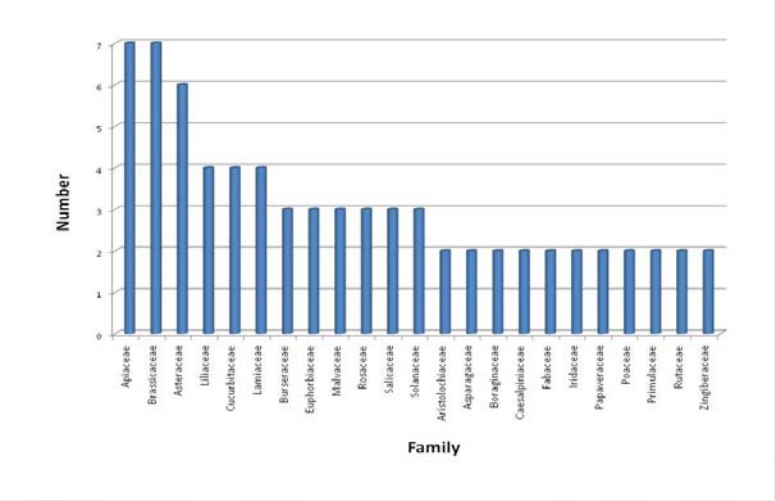

Fig.2. Main plant families used in gout treatment.

Taken together, 156 remedies were made by these 109 plant species, sixty-six of the plant species being used only externally, and twenty-seven only internally. However, seventeen plants had both internal and external applications. Interestingly, 106 remedies were used externally (68.4%), and 49 remedies were used internally (31.6%). The local anti-inflammatory and/or analgesic effects were exerted by the plants used externally, and the plants used internally were useful for their systemic anti-inflammatory effect, system-

37- Adams et al., 2009: 343-359.
38- Nguyen et al., 2004: 1414-1421.
39- Kong et al., 2000: 199-207.
40- Owen et al., 1999: 149-160.

ic analgesic effect or the reduction of bad humors (maybe by uricosuric or xanthine oxidase inhibitory effects). Some plants were used topically and internally to take advantage of local and systemic activities.

Salve/*Zomaad* in Persian/ was the main dosage form (54) of the remedies. After *zomaad*, crude herb (41), gold /*talaa* in Persian/ (19 drugs), oil (12), and tabikh (11) were the main methods for drug preparations (Fig.3). *Zomaad* was usually an oily based topical form that remains on the painful site for a long time. Evidence has suggested that the exposure of the damaged skin to the oily substance may trigger good drug penetration.

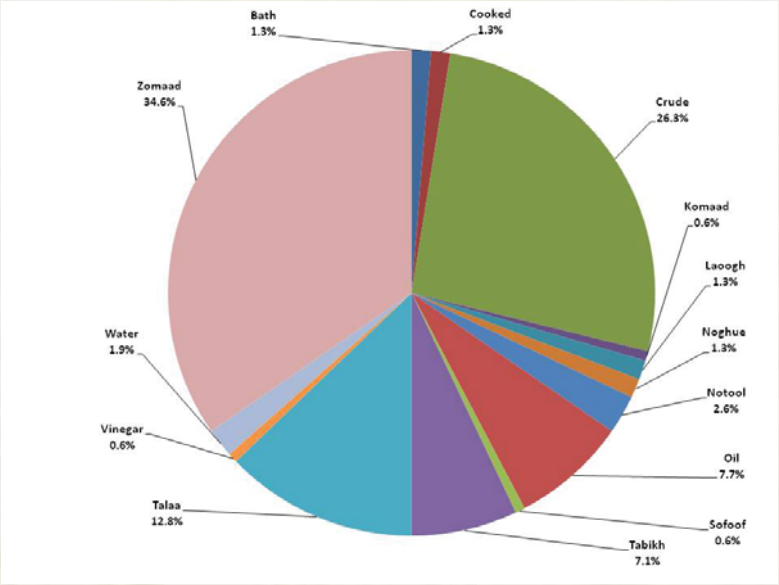

Fig.3. Percentage of preparation methods for herbal gout remedies.

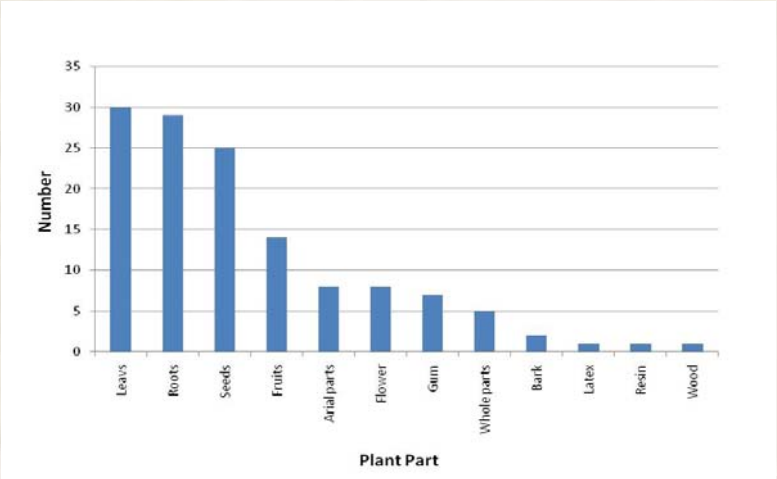

*Fig.4. Plant parts which used for herbal gout remedies pre*paring.

Twelve different plant parts were used for remedy preparation. In total, leaves (22.9%), roots (22.1%), and seeds (19.1%) made up 64.1% of all plant parts (Fig. 4).

According to TIM (like humoral medicine, as a kind of traditional medicines), each substance has its own nature, which can be hot, cold or moderate and wet, dry or moderate. In addition, each quality is subdivided into four degrees, and a higher degree equates decreased nutritive characteristics and increased medicinal properties. Drugs, which belong to the 4th degree, are categorized as poisons. To correct the imbalance existing in the body at the time of disease, the medicine used should have an opposite nature to the disease and be of a suitable degree.[41, 42] Taken together, In this study, 75.5% of the plants had a hot nature and 21.8%, a cold nature. In addition, 85.5% of the plants were dry and 13.6% wet. The rest of the herbs had a moderate nature (Fig. 5). Overall, the main categories of the drugs used to treat gout were hot and dry in the 2nd degree (26 species), hot and dry in the 3rd degree (20 species) and hot in the 2nd and dry in the 1st degree (9 species). In total, 75.0% of the plants had a hot and dry nature. This result was completely expected because TIM classified gout as a disease having a cold and wet nature.

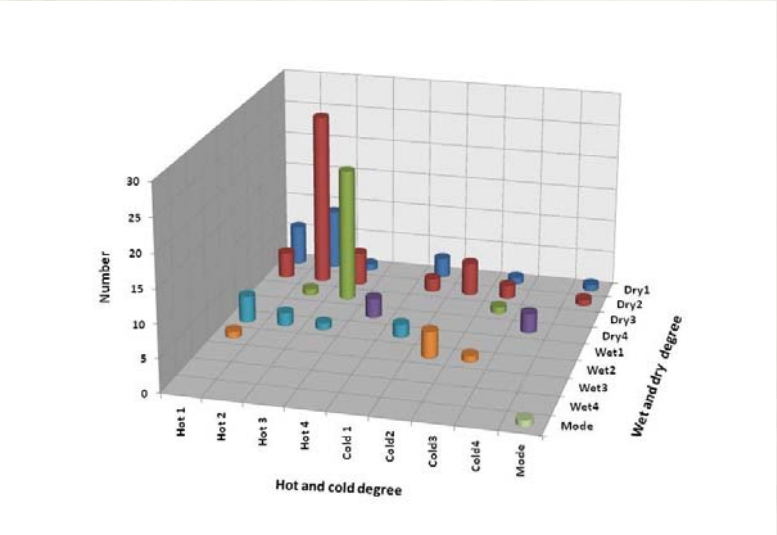

Fig.5. Plant species nature used as gout remedy.

Different excipients were used for drug preparation. Examples were vinegar (16 examples), wines (10 examples), honey (5 examples), fenugreek flour (4 examples), wax or oil (4 examples) and milk (3 examples). According to traditional Iranian pharmacy, excipients were added for their additive/synergistic effects, better drug delivery or reducing/masking

41- Aghili Shirazi, 2009.
42- Jackson, 2001: 487-489.

unwanted effects. Vinegar is also a gout-healing drug, and honey and wine were common excipients in gout and rheumatism remedies from European traditional medicine. Moreover, fenugreek was a rheumatism drug in Europe.[43]

Out of the 109 species reported in Table 1, three plants are endemic to Iran: the *Dorema ammoniacum*, the *Ferula persica* and the *Ajuga chamaecistus*. Most of the plants (77 species) are native to Iran and have a wide distribution. Twenty-nine plant species were non-native to Iran; however, six of these species were cultivated in Iran. Out of the 23 plants that were non-native species, nine species were being imported; hence they are now available in Iran's rational herbal medicinal markets.[44, 45]

Thirty-seven plant species were mentioned in at least three references. This meant that they had remained in the medical system as treatments for gout for a long time, and different physicians confirmed their effectiveness in different periods (Fig. 6). For instance, *Paeonia officinalis*, *Papaver somniferum*, *Salix alba*, *Populus alba* and *Elettaria cardamomum* were reported in all five references. Of course, one might speculate that some of the plant recipes were copied from one text to the other without healers ever having used the remedy. To investigate this claim, all of the drugs mentioned for gout in each book were compared to the others (Fig. 7). This figure rejected the above speculation because the later manuscripts did not replicate the preceding ones. Therefore, we concluded that if a drug was mentioned in a reference for a specific disease, it meant that either the author tested it himself, or the drug was so popular that whose effect was known and hence its reexamination was not needed. If an author did not mention a drug that had previously been mentioned in other references, then we could conclude that he did not observe the desired activity for that drug or did not even investigate the particular drug. This latter point is less likely since the Greco-Roman texts were classified as the main references among Iranian medical practitioners. In our study, we found that some of the drugs previously mentioned by Dioscorides for gout were also present in Iranian texts. Nevertheless, some other Dioscorides remedies were not used by Iranians, and new drugs were introduced instead. We may now speculate that if some drugs for specific diseases have persisted for a long time, they can have a lot of potential for future investigations.

43- Adams et al., 2009: 343-359.
44- Amin, 2005.
45- Hooper et al., 1937.

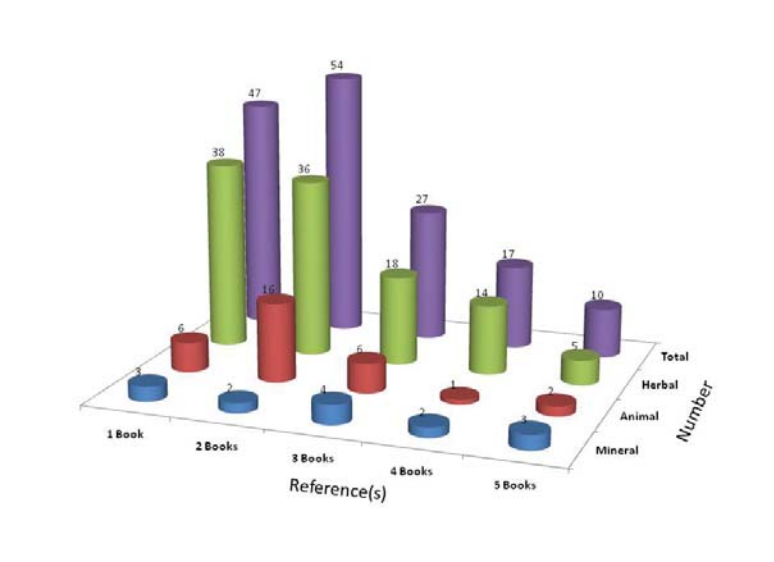

Fig.6. Repetition of gout remedies in traditional Iranian medicine references.

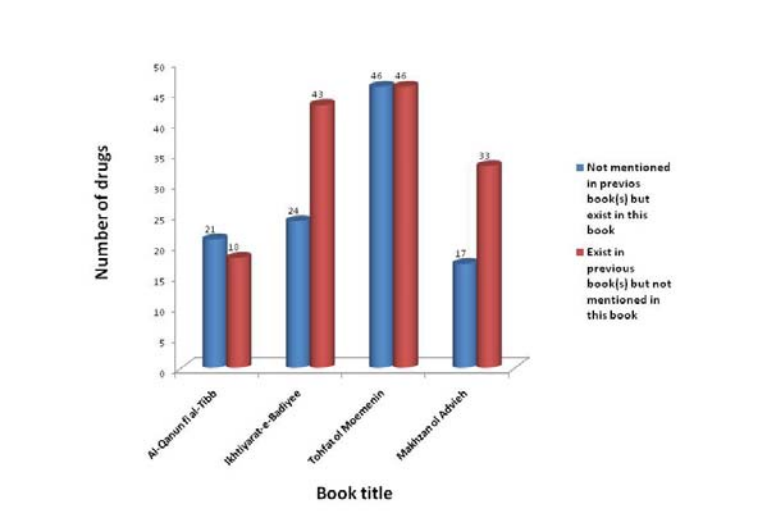

Fig.7. Number of drugs that were added or omitted in each book (Al Hawi, which is the oldest one, is considered as the base).

It is worth mentioning that some of the plant species used in TIM for the treatment of gout have also been used to treat gout in other countries. The following list contains the name of some plants used in the treatment of gout as well as the name of countries where they have been administered as remedies: *Sambucus nigra* in Britain, Lebanon, Italy and Spain;[46- 50] *Vitis vinifera* in India, Italy, and Lebanon;[51- 54] *Verbena officinalis* in Lebanon and China;[55, 56] *Cichorium intybus* in India and Canada;[57, 58] *Brassica oleracea* in Europe and Korea;[59, 60] *Olea europea* in Lebanon and Italy;[61, 62] *Viscum album* in Lebanon and Europe;[63, 64] *Verbena officinalis*

46- Allen et al., 2004.
47- Benítez et al., 2010: 87-105.
48- De Natale et al., 2007: 295-303.
49- Leporatti et al., 1990: 213-223.
50- Marc et al., 2008: 315-334.
51- Guarrera, 2003: 515-544.
52- Khare, 2007.
53- Marc et al., 2008: 315-334.
54- Passalacqua et al., 2007:
55- Kong et al., 2000: 199-207.
56- Marc et al., 2008: 315-334.
57- Khare, 2007.
58- Owen et al., 1999: 149-160.
59- Adams et al., 2009: 343-359.
60- Kim et al., 2006: 7-16.
61- Leporatti et al., 1985b: 65-68.
62- Marc et al., 2008: 315-334.
63- Adams et al., 2009: 343-359.
64- Marc et al., 2008: 315-334.

in Lebanon and China;[65, 66] *Ricinus communis* in Nepal and India;[67, 68] *Citrullus colocynthis* in Europe and Tunisia;[69, 70] *Populus alba, Hordeum vulgare, Lemna minor, Capparis spinosa, Hypericum perforatum, Inula helenium, Matricaria chamomilla, Heliotropium europaeum,* and *Lavendula stoechas* in Europe;[71] *Aquilaria agallocha, Cassia fistula, Ficus carica, Indigofera tinctoria, Piper longum* and *Salix alba* in India;[72- 75] *Peganum harmala* and *Vicia faba* in Lebanon;[76] *Calluna vulgaris* in Portugal;[77] *Apium graveolens* in Italy;[78] different *Aristolochia* species widely used in Japan, Brazil, Libya, India, China, Mexico, the Andes, North America and Europe;[79, 80] *Ajuga* species widely used in various countries;[81, 82] *Plantago ovata* in India;[83, 84] and the juice of *P. lanceolata* and *P. major* taken with wine or honey in Europe.[85]

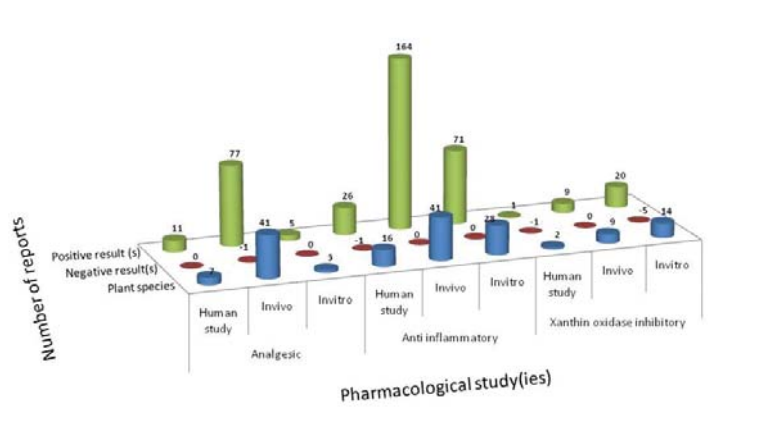

Fig.8. Number of related pharmacological activity reports for plant remedies mentioned in Table 1 (-: negative result(s)).

Table 1 (Fig.8) presents the data collected from at least one pharmacological study on gout (anti-inflammatory, analgesic, or xanthine oxidase inhibition) for 68 out of the 109 plant species. In terms of xanthine oxidase inhibition, 14 of these plant species have shown *in vitro* activity, nine have shown *in vivo* activity and two have shown results in human studies. In other *in vitro* experiments, 28 of these plants have shown anti-inflammatory effects, and three analgesic effects. *In vivo* studies have shown anti-inflammatory and analgesic effects for 44 and 42 of the 109 plant species, respectively. In human studies, 17 plant species have shown anti-inflammatory effects, and eight analgesic effects. Because one study is not enough to prove the effectiveness of a drug, we have concluded that plants that have been examined in at least three studies *(in vitro* or *in vivo*) can be studied in the next stage

65- Kong et al., 2000: 199-207.
66- Marc et al., 2008: 315-334.
67- Manandhar, 1998: 199-206.
68- Parveen et al., 2007; 387-399.
69- Adams et al., 2009: 343-359.
70- Marzouk et al., 2010: 15-19.
71- Adams et al., 2009: 343-359.
72- Dymook et al., 1893.
73- Gruenwald et al., 1998.
74- Khare, 2007.
75- Williamson, 2002.
76- Marc et al., 2008: 315-334.
77- Neves et al., 2009: 270-283.
78- Leporatti et al., 1985a: 53-63.
79- Dymook et al., 1893:
80- Heinrich et al., 2009: 108-144.
81- Israili et al., 2009: 425-462.
82- Khare, 2007:
83- Dymook et al., 1893:
84- Gruenwald et al., 1998:
85- Adams et al., 2009: 343-359.

(either *in vivo* or human studies).

We did not find any information about the uricosuric activity of the plant species listed in Table1. Therefore, we did not insert a column for this activity. However, we did find in vivo studies indicating that *Glossostemon bruguieri* reduced levels of urea, creatinine and uric acid in rats.[86] In another *in vivo* study, *Aristolochia indica* extracts were found to inhibit drug-induced hyperuricemia in rats.[87] The mechanisms of these functions, however, were not mentioned.

In addition to plants, some natural medicines taken from animals or minerals were reported to be suitable for gout treatment. Despite little pharmacological information about these remedies, we found some interesting points for some cases.

In total, 31 different animals were found. Meat was the most usable part, followed by skin and suet. In fact, 87.0% (47 remedies) of remedies from animals were used topically (Table 2). Oysters with elements like zinc and selenium possessed antioxidant properties that might be useful in gout treatment.[88, 89] Another example was rabbit's meat, having a high concentration of Omega-3 fatty acids with potent anti-inflammatory effects.[90, 91]

Twenty remedies for gout were made from 14 mineral substances, 90.0% of which were applied topically (Table 3). An interesting remedy from this group was smoke inhalation of coal, which occurred via nasal delivery. The other example was the sulfurated mud which was shown to elicit analgesic effects [92] and was believed to be effective for rheumatic diseases.[93] Moreover, mud was also considered to have anti-inflammatory effects.[94] Gold another anti-gout drug mentioned in traditional textbooks, and sodium aurothiomalate was an antirheumatic drug[95] suppressing inflammation processes and inhibiting cyclooxygenase II.[96]

Aghili Shirazi mentioned a kind of mushroom from Polyporaceae family, *Polyporus officinalis* Fries. (Gharighoon in Persian), for gout treatment. It was used externally in talaa form.

In addition to the findings mentioned above, this review has identified some topics that could be of particular interest for future research:

• Studies on plant species belonging to Asteraceae, Apiaceae and Lamiaceae, which are widely used for gout remedies in different traditional medicine systems and cultures.

• Investigations of plants where no related pharmacological information is available:

86- El-Sayed et al., 2004: 186-189.
87- Ramachandran et al., 2009: 304-308.
88- Powell, 2000: 1447-1454.
89- Burk, 2002: 75-79.
90- Tassinari et al., 2002: 119-124.
91- Simopoulos, 2002: 495–505.
92- Kristof et al., 2000: 233-236.
93- Pratsel et al., 1992: 37-41.
94- Giacomino et al., 2007: 352-353.
95- Yokoyama, 1999: 683-687.
96- Nieminen, 2008: 309-316.

o External uses of *Rumex acetosa, Populus alba, Lemna minor, Prangos ferulacea, Arum italicum, Lens culinaris* and *Vicia faba* has been mentioned in at least three references. *In vitro* pharmacological studies for local anti-inflammatory or analgesic effects will be beneficial.

oAt least three authors have confirmed the effectiveness of ingestion of *Ajuga chamaecistus, Paeonia officinalis* and *Euphorbia lathyris. In vitro* pharmacological studies for their systemic effects may lead to interesting results.

o *Glossostemon bruguieri, Aristolochia indica* and *Alkanna tinctoria* have been effective both internally and externally, and they can lead to *in vitro* studies.

• From the perspective of using a specific drug in different cultures, the following drugs are used in more than three regions and deserve more research:

o*Sambucus nigra,* which is used in five civilizations, and *Vitis vinifera,* which is used in four countries.

o Different *Aristolochia* and *Ajuga* species, which are used in many civilizations.

• In addition to being cited in at least three references, the following plants Have been used in three or more pharmacological studies that have confirmed their effects. Thus, future studies for their use in gouty conditions can be beneficial.

o The following plants can be beneficial for anti-inflammatory activity: *Olea europaea* (with 4 *in vivo* reports); *Hordeum vulgare* (with 1, 2 and 5 *in vitro, in vivo* and human studies results, respectively); *Withania somnifera* (with 4, 11 and 1 *in vitro, in vivo* and human studies results, respectively); and *Vitis vinifera* (with 2, 1 and 1 *in vitro, in vivo* and human studies results, respectively).

o *Withania somnifera* L. (with 5 *in vivo* studies) can be beneficial for analgesic activity.

o *Vitis vinifera* L. (with 2 *in vitro* and 1 *in vivo* reports) can be beneficial for xanthine oxidase inhibition.

Ethnopharmacological leads can be standardized herbal preparations rather than single chemical entities, and they are highly attractive to companies interested in herbal medicines.[97] One of the important approaches in ethnopharmacy is an investigation of the traditional formulation in a pharmaceutical view.[98] Therefore, in an ethnopharmaceutical in-

97- Heinrich et al., 2001: 108-144.
98- Heinrich, 2008.

vestigation, preparation techniques, dosage forms, and methods of extraction should be meticulously examined.[99] For example, nearly 50 dosage forms exist in traditional Iranian pharmacy, and the preparation method for each form is not just a simple mixing of some materials. Nevertheless, ethnopharmaceutical evaluations cover valuable pharmaceutical details like particle size of each ingredient, shelf life of drug, organoleptic characteristics, route and duration of administration. A precise survey of the pharmaceutical characteristics of each dosage form could be helpful not only in preparing the correct fraction for pharmacological studies but also in drug formulation and manufacture.

The authors of the old medical texts were aware of the toxicity of plants like *Rhus albida, Conium maculatum, Brassica nigra, Croton tiglium* and *Alium xiphopetalum*. Authors warned about the low therapeutic index and dangers of using some plants like *Conium maculatum*. In the case of *Colchicum autumnale,* the authors mentioned that it had strong side effects on the gastrointestinal system, and antidotes for this herb were tragacanth, sugar, and saffron.

We could not find any relevant pharmacological studies for 45 plant species. However, it seems that phytochemical data have shown their potential for further *in vivo/in vitro* studies. For example, the major chemical constituent of *Aristolochia indica* is aristolochic acid, which plays a regulatory role in prostaglandin synthesis and inhibits inflammation by immunological and non- immunological activities. The mechanism is thought to be direct inhibition of phospholipase A2, decreasing the generation of eicosanoids and platelet-activating factors. Another inflammatory mechanism may be the effect on arachidonic acid mobilization in human neutrophils.[100] In addition, in vivo studies with *Alkanna tinctoria* have shown that shikonin and alkannin efficiently reduce inflammation,[101- 105] and γ-linolenic acid, which has potent anti-inflammatory properties, is a precursor of prostaglandin E1.[106] Rutine and vitexin (flavonoids of *Rumex acetosa*) have anti-inflammatory and lipo-oxygenase inhibitory properties .[107] Moreover, most of the highly cited herbs mentioned in TIM books contain secondary metabolites like flavonoids, coumarins, phytosterols and phenolic acids, which possess xanthine oxidase inhibitory activity.[108- 111] Furthermore, although xanthine oxidase inhibition has not been studied in some species of plants, other species in the same genus have shown xanthine oxidase inhibition. These genera include *Fi-*

99- Ibid
100- Williamson, 2002:
101- Assimopoulou et al., 2004: 433-438.
102- Gao et al., 2000: 2561-2569.
103- Kourounakis et al., 2002, 262-266.
104- Sekine et al., 1998: 133-139.
105- Su et al., 2008: 813-822.
106- Papageorgiou et al., 2003: 251-258
107- Duke et al., 2001: 813-822.
108- Chang et al., 1994: 501- 506
109- Chang et al., 1995: 1969-1973
110- Chang et al., 1993: 2165-2170
111- Ibid

cus, Ajuga, Panax, Aristolochia, Cuscuta, Liquidambar, Smilax, Piper, Plantago, Paeonia, Prunus, Citrus, Verbena, and *Cuscuta*.[112- 114] Therefore, it seems that ethnopharmacological studies based on traditional uses and phytochemical data will yield valuable results.

A number of commonly cited plants in TIM for gout and rheumatic disorders (e.g., *Salix alba, Zingiber officinale,* and *Papaver somniferum*)are still used today in folk, alternative, and modern medicinal practices. Colchicum *autumnale* is another good example because it has been successfully used in both TIM and conventional medicine. Other plants practiced in TIM (e.g., *Dorema ammoniacum, Aristolochia indica, Ferula persica, Panax ginseng, Citrullus colocynthis, Croton tiglium* and *Senna italica*) are similar to *Colchicum autumnale* in terms of their nature and therapeutic properties and hence are good candidates for future studies.

Many cultures believe in the hot and cold system and divide their traditional drugs into hot or cold. Because of its widespread use in all continents, this system can be a valuable topic in ethnopharmacological studies. Unfortunately most published studies (even field ones) have neglected this concept. Thus, we suggest that the inclusion of this issue in historical studies can be beneficial. Furthermore, the exact mechanism of hot and cold medicine is still unknown, and future studies should investigate this mechanism. The other issue is that although humoral medicine is the basis of traditional medicine in the Middle East, Europe, Asia Pacific, and the Indian Subcontinent, most of its principles are foreign to modern scientists. Systemic investigation on its philosophy, therapeutic methods, and terminology can be helpful to properly direct ethnopharmacological studies of these regions.

Conclusions

With the absence of traditional knowledge in modern society, the written historical record becomes increasingly important. Scientific examination of historical works can be the basis for the "rediscovery" of long forgotten remedies as well as a source of information for a more focused screening of new leads. Medicines that have been used for thousands of years may provide important new avenues for pharmaceutical research. Therefore, this study has sought to urge researchers to collaborate across disciplines to better understand and exploit the historical record of traditional medicine in Iran.

In this review, we have seen that a number of remedies rec-

112- Kong, 2000: 199-207.
113- Sweeney, 2001: 273-277.
114-Umamaheswari, 2007: 547-551.

ommended for the treatment of gout in TIM have actually shown certain activities in assays relevant to their traditional usage, and some of these remedies are still in use today. In some cases, active constituents have been isolated and further information has been gained on mechanisms of action. Moreover, plants that have not been tested yet may be promising drug candidates. Continuing research is necessary to elucidate the pharmacological activities of natural remedies used to treat gout.

The ancient history in medicine and richness of plant sources are the strong backbone of TIM. Over several thousand years in Iran, the traditional medicine has built up a characteristic medical system. Traditional Iranian medicine has the potential to be a very rewarding source of medical and medicinal knowledge. Special focus should be applied to drugs and therapeutic methods. Because modern biomedical research pays little attention to TIM, it is important to conduct systematic studies of the remedies found in TIM references.

This survey was the first work carried out by the Traditional Pharmacy Department of Shiraz Faculty of Pharmacy (as the first department of Traditional Iranian Pharmacy) investigating TIM books. For a number of reasons, in this study, we focused on remedies used for gout. Firstly, gout is a historical disease that is still widespread in Iran as well as in the rest of the world. Moreover, it seems that gout described in TIM is comparable to that described in modern medicine (see introduction). In addition, numerous remedies have been used to treat gout in TIM. Furthermore, the mechanisms of gout and gouty pains are almost clear, and some in vivo and *in vitro* test systems have been established in this field. Thus, a meaningful pharmacological study of remedies is possible.

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