

INTERNATIONAL JOURNAL OF UNANI AND INTEGRATIVE MEDICINE



E-ISSN: 2616-4558
P-ISSN: 2616-454X
IJUIM 2021; 5(1): 30-35
Impact Factor (RJIF): 6.3
Peer Reviewed Journal
Received: 16-12-2020
Accepted: 18-01-2021

Dr. Atqia Asnah
PG Scholar, PG Department of
Moalijat, Govt. Nizamia Tibbi
College, Hyderabad,
Telangana, India

Dr. Mohd Ahsan Farouqi
I/c HOD, PG Department of
Moalijat, Govt. Nizamia Tibbi
College, Hyderabad,
Telangana, India

Dr. Ghousia Tabassum
PHD Scholar, Department of
Biotechnology, Jamia Millia
Islamia, New Delhi, India

The relation between gouty arthritis and menopause: A Unani conceptual review

Dr. Atqia Asnah, Dr. Mohd Ahsan Farouqi and Dr. Ghousia Tabassum

Abstract

Menopausal stages are progressively associated with an increased prevalence of hyperuricemia, especially from the late transition stage. This association was independent of age and other confounders, indicating menopausal stage per se as an independent risk factor for hyperuricemia. Estrogen has uricosuric properties and with its decline the menopausal women are prone to gouty arthritis. Hormone replacement therapy is touted as the best treatment to problem of gout in menopause. However, HRT isn't without risks. In fact, it has been linked to an increased risk of breast cancer, heart disease, osteoporosis and stroke. The side effect of the therapy shows immense responsibility of the alternative medicine to create awareness for the particular aspect. Unani medicine has a variety of safe and effective drugs for the management of Nigris(Gout) in Menopause. And it has been successful in treating this disease since a long time without any unwanted effects.

Keywords: gout, gouty arthritis, hyperuricemia, *Nigris*, menopause, hormone replacement therapy, Unani medicine

Introduction

Until the early 1800s, uric acid was thought to be a biologically inert waste product, but hyperuricemia is increasingly considered a potential risk factor for various chronic conditions such as chronic kidney disease, cardiovascular disease, and metabolic syndrome, and has a well-established causal role in gout [8]. Menopausal stages were progressively associated with an increased prevalence of hyperuricemia, especially from the late transition stage. This association was independent of age and other confounders, indicating menopausal stage per se as an independent risk factor for hyperuricemia.

Menopause, a form of reproductive aging, is defined as the permanent cessation of ovarian follicular activity and eventually, the menstrual cycle. Normally, menopause is a natural process of the body; however, it can be the result of other causes such as surgery, chemotherapy, or iatrogenic insult.

Additionally, two hormones (progesterone and estrogen) integral to reproductive aging are no longer produced during menopause. Specifically, the decline and eventual cessation of estrogen production has been shown to cause a variety of symptoms during menopause, affecting each woman differently [25].

Aims and Objectives

- To propagate the safety and efficacy of Unani medicine in the Menopausal women suffering from Gout.
- To create awareness of side effect free asset of USM (Unani system of medicine)

Review of literature

One of the five aphorisms of Hippocrates on gout is.. "A woman does not take the gout, unless her menses be stopped" [22].

Causative factors playing role linking gout and menopause

Estrogen

During the menopausal transition, changes in estrogen and progesterone levels affect not only vasomotor symptoms, sexual dysfunction, osteoporosis, and cardiovascular disease (CVD), but also uric acid level.8 Estrogen not only plays a pertinent role in the female reproductive system, but also induces a variety of beneficial effects in other areas of the body.

Corresponding Author:
Dr. Atqia Asnah
PG Scholar, PG Department of
Moalijat, Govt. Nizamia Tibbi
College, Hyderabad,
Telangana, India

Specifically, this hormone increases hepatic production of binding proteins like sex hormone binding globulin, maintains appropriate fluid balance in the body by allowing for salt and water retention, promotes coagulation, and it allows for a favourable lipid profile via increases in high density lipoprotein (HDL) and decreases in low density lipoprotein (LDL) [25].

Estrogen and progesterone have a beneficial effect on how uric acid is cleared by the body, so the drop in these hormones when menstruation ends eliminates any protective effect. Gout occurred most often in women who had surgical menopause with sudden complete removal of hormone function. The age of the first period, as well as illnesses, athletic activity and eating disorders can also affect the risk of gout in women [11].

An association between menopausal status and hyperuricemia has been previously examined. A study using the Third National Health and Nutrition Examination Survey showed a positive and independent association of menopause with hyperuricemia and gout. In another study, menopause was independently associated with a high level of uric acid after adjustment for age and body mass index (BMI).

Since an increase in follicle stimulating hormone (FSH) is a landmark feature of perimenopause followed by a decrease in estradiol, the increased prevalence of hyperuricemia after menopause indicates that the female sex hormone may have protective effects against hyperuricemia.

Menopausal stages were progressively associated with an increased prevalence of hyperuricemia, especially from the late transition stage. Many studies have shown that there's a rapid decline in estradiol occurring in the late in the transition period of menopause. The Bio Cycle Study has shown an inverse relationship of progesterone with uric acid level, whereas Estradiol is reported to play a more important role than progesterone in the gene expression of uric acid transporters (Urat1, Glut9, and Abcg2) in the mouse kidney. The imbalance of estrogen and progesterone may explain the change in uric acid during the transition period [8].

A better understanding the relationship between menopausal stage and hyperuricemia helps for identifying optimal timing for preventive measures for hyperuricemia.

Oxidative Stress

In healthy, premenopausal women there is usually an appropriate balance between free radical species and antioxidant mechanisms. As such, the level of oxidative stress in these women is not sufficient enough to affect the ovaries until the onset of menopause. Menopause creates a pro-oxidant state in the body due to the decline of the natural antioxidant, estrogen. Specifically, studies have reported that oxygen radicals have an important physiologic role within the ovary [25].

Obesity

Obesity is related to an increased risk of menstrual disorders and decreased fertility in premenopausal women, and to increased cardiovascular risk in postmenopausal women. The prevalence of obesity, which is a risk factor for hyperuricemia, increases during the menopausal period [8].

Unani concept of Menopause

Unani system of medicine is enriched with the concept of

Ihtibas-i-Haiz (amenorrhoea) but there is no exact description of menopause, nevertheless it may revealed under Ihtibas al-Tamth and can be correlated with Sin-i-Yaas (age of natural termination of menstruation).

Basic fundamentals of Unani system divide human life into four stages which are as follows.

Sinn-i-Numu (up to 30 years of age, Har-RatabMizaj)

Sinn-i-Shabab (30-40 years of age, Har-YabisMizaj)

Sinn-i-Kuhulat (40-50 years of age, Barid-RatabMizaj)

Sinn-i-Shaykhukhat / Sin-i-Yas (above 50 years of age, Barid-YabisMizaj) [1].

Tabai Sin-i-Yasis attained at the age of 50 years, sometimes 60 years [1]. As menopause usually begins between the ages of 45 and 55 and specially the late transition stage, it is bound to come under Sinn-i-Shaykhukhat which is Barid Yabis in Mizaj (temperament). As Barid Yabis temperament is the quality of Khilt-i-Sawda' (black bile), we may infer that at this stage excess of Khilt-i-Sawda' developed in the body, makes less production of Rutubat-i-Unsurya ultimately decreases the Hararat-i-Unsurya and finally all Quwa (powers) of the body gets decreased [6].

Etiology

Zakariya Al Razi (Rhazes)(865 – 925 AD) maintains that menstruation ceases due to dominance of Barid (cold) and viscous Akhlat (humours) near the vicinity of uterus or its vessels due to obstruction or increased viscosity of blood. Ibn Sina stated it is the weakness of Quwate Dafiya (faculty of excretion) of the body which alter the normal cycle and ultimately stop [20]. Other causes of Ihtibas al-Tamth as described by various unani scholars are liver disease and obesity as blood vessels becomes narrow reducing the blood flow [6, 27, 29].

Incidence of Gout in Women

The prevalence of self-reported physician-diagnosed gout based on the Third National Health and Nutrition Examination Survey (NHANES-III) was 3.5% in women ages 60–69 years, 4.6% in women ages 70–79 years, and 5.6% in women ages 80 years [10]. The incidence of gout has doubled among women over the past 20 years, according to the Rochester Epidemiology project study [11].

Prevalence

The prevalence of gout is found to have increased in recent years. It is rare in children and premenopausal women. [5] The epidemiological data showed that the incidence and prevalence of gout had more than doubled in last forty years. According to UK General Practice, the prevalence of gout is roughly 1.4% while serum urate levels more than 7 mg/dl are found in up to 18% of the population. The incidence of gout varies in the population with an overall prevalence of less than 1 to 15.3%. The prevalence increases substantially with age and increasing serum urate levels. For serum

urate values greater than 9 mg/dl, the cumulative incidence of gout reaches 22% after 5 years. Hippocrates had particularly mentioned that-gout is very common in men but maybe seen in women after menopause [2].

Classification of gout [5, 13, 17].

1. On the basis of Humors (Akhlat) involved
 - a. Single humors dominance
 - i. Damwi (Sanguineous)

- ii. Safrawi (Bilious)
- iii. Balghami (Phlegmatic)
- iv. Saudawi (Melancholic)
- b. Combined humors dominance
 - i. Dam-e-Safrawi
 - ii. Dam-e-Balghami

Etiology

Majority of the Unani scholars have considered the basic cause of Niqris to the following factors:

- Sue mizaj sazij (Simple imbalance of temperament) ^[5, 15].
- Sue mizaj maddi (Imbalance of temperament due to change in matter): It is the main etiological factor. It is an abnormal temperament where homeostasis of body is disturbed due to alteration in the specific ratio of Kammiyat and Kayfiyat (Quantitative and Qualitative changes) of akhlat (maddah) locally or generally ^[5, 19].
- Weakness of joints, which result in accumulation of causative matter (maddah-e-Niqris) in the joint and thus leading to the development of Niqris. ^[5, 16, 19]
- The important predisposing factors responsible for the development of Niqris are excessive eating, excessive drinking, sedentary lifestyle, heredity, luxurious and unethical living and lack of exercise ^[5, 19, 29].

Etiopathogenesis of the Disease (Gout)

The Unani System of Medicine is based on the Hippocratic doctrine of four humors (Akhlat) i.e Blood (Dam), Phlegm (Balgham), Bile (Safra) and Black bile (Sauda). A proper balance of Akhlat within the body is essential to maintain optimum health. According to Unani System of Medicine, diseases are due to the disproportionate distribution of humors or Akhlat inside the body. These humors, which are out of proportion (quantity and quality), collect in various parts of body, at times producing inflammation, and are often root cause in the origin and development of a particular illness, one of them being Niqris. In case of Niqris, the humors collect in the joint, thereby leading to pain, swelling and other articular damage ^[4, 21].

According to Hakeem Kabeeruddin gouty matter (noxious matter causing gout/maddah-e-Niqris) is basically a byproduct of liver metabolism, and it look likes the urinary calculus to a large extent. Niqris is one of those disease, which is related to the hepatic and tissue metabolism (hazm-e-kabidi or hazm-e- chaharum) ^[13].

According to Nuh Al Qamri the author of famous book "Ghina Muna" Niqris occur due to dissemination of that matter towards the extremities, which is repulsed by the vital organs (due to strong power) and accepted by extremities (due to their weakness). The matter is formed as a result of disturbed Quwwat-e- Hazimah (Digestive Power) due to dysfunctioning of liver ^[16].

The active cause of Niqris(Gout) is Sue Mizaj and Raddi Mawad (morbid materials) ^[17].

Niqris (Gout) is produced when the madda spells (falls) towards the lower extremities, expelled by the Vital Faculties (AzaaeRaisa) of the body towards these extremities, which are not able to expel these matters ^[23].

As such, when propulsive power of the body (Quwwat-e-Dafiyah) tries to expel this matter, a part of it still remain in the body, which accumulate at various anatomical locations

(joints, kidney etc.) and produce various clinical features. Simultaneously, the blood and urine level of this substance are also raised ^[24].

Avicenna (Ibn-e-Sina)(980-1037AD) in his famous book "Alqanoon fit Tibb" said that, the matter liable for Niqris may be blood (Dam) alone or blood mixed with phlegm (Dam-e-balghami), or blood mixed with yellow bile (Dam-e-safrawi), or blood mixed with black bile (Dam-e-saudawi) or it may be phlegm (balgham) alone or raw phlegm (balghamkham) alone or serous humor (mirrah) alone or a mixture of humors. But in majority of cases this matter is of serous phlegmatic type (balgham-e-mirrah) ^[28].

Modern Treatment

Hormone replacement therapy (HRT) can make a big difference in counteracting these symptoms by replacing the diminished hormones in a natural way. However, HRT isn't without risks. In fact, it has been linked to an increased risk of breast cancer, heart disease, osteoporosis and stroke. You should carefully consider these risks before deciding if HRT is the best treatment option for your symptoms.

While some health benefits are linked to HRT, several risks are associated with it as well as it has a wider range of secondary health complications like vaginal bleeding, breast cancer, endometrial cancer, gallbladder diseases etc ^[10].

Risks of Hormone Replacement Therapy

HRT has been connected to an increased risk for certain types of cancers, especially breast cancer.

The studies that discovered a link between HRT and breast cancer refer to women being treated with synthetic HRT, not bioidentical HRT. However, there are no studies that show that bioidentical HRT is any safer than synthetic HRT. The risk of breast cancer increases the longer a woman engages in any type of HRT, and the risk decreases once HRT is stopped.

A higher risk for uterine cancer also exists when menopausal women with a uterus use estrogen HRT only. This is why doctors will generally prescribe progesterone along with estrogen. With a history of hysterectomy, progesterone is foregone and only estrogen is advised.

Other risks for women undergoing HRT include osteoporosis and stroke. Osteoporosis is particularly prevalent among postmenopausal women, which is why synthetic HRT is now mostly used for short-term relief of menopause symptoms. Many women reject the risks associated with hormone replacement therapy to treat their menopause symptoms and, instead, seek relief from alternative sources.

Unani treatment

The Unani principle of management of disease is to correct the altered temperament. Therefore, before commencing any treatment, Mizaj of a patient or organ has to be evaluated. Gout in symptoms in Menopause can be corrected by following approach.

1. Ilajbil-Ghiza
2. Ilajbid-Dawa
3. Ilajbit-Tadbeer

Ilaj Bil Ghiza (Dietotherapy)

The treatment of Su' Mizaj includes the use of food items having the temperament exactly opposite to the temperament of disease. This is called Ilaj- bil- zid. As the

mizaj of menopausal women is Barid yabis so food items having Har ratib mizaj will be helpful. For this purpose dry fruits are very helpful ^[15].

Dietary Recommendations

1. Estrogen rich foods like nuts, almonds which are known to possess uricosuric action ^[10].
2. Soy products have isoflavones that are known to boost the estrogen levels in women.
3. Almonds, cashew nuts, peanuts, oats, corn, wheat and apples all showed estrogenic activity ^[30].
4. Antioxidants like cherries and black berries. Cherry being high in vitamin C helps in increase excretion of uric acid in urine.
5. Secretion from stomach and intestine must be excreted out by using mild laxatives. Beet root and spinach are especially advised in meals as these are good laxatives.

Dietary Restrictions

1. Red meat
2. High sugar intake
3. High purine food intake eg fishes like Tuna, sardines.
4. Alcohol consumption is a particularly common factor in promoting hyperuricemia by increasing urate production.
5. The food items which produce flatulence should be avoided. For example cauliflower, brinjal, kathal, arvi etc. These all are called as Badi ghizayen.

ILAJ BID DAWA (Pharmacotherapy)

They are various drugs in the unani Medicine for the Gout arthritis in the menopausal Women. Some of the drugs description and mode of action is given below:

Colchicum autumnale

Colchicine works by decreasing swelling and lessening the buildup of uric acid crystals that cause pain in the affected joint. Colchicine has been shown to reduce oxidative stress by reducing calcium (Ca^{2+}) influx into neutrophils ^[18]. Menopause is known to create a pro-oxidant state in the body due to the decline of the natural antioxidant, estrogen. Colchicine not only acts as anti inflammatory for the affected joint but also as an antioxidant which is very helpful for menopausal women. Other effects of colchicine include inhibition of cancer cell migration and metastatic potential in malignancies ^[7]. It has been associated with a delay in the age of onset of leukemia in a study done on rats ^[14].

Black cohosh (Actaea racemosa)

Black cohosh is among the most popular and longest-studied natural hot flash remedies for women who don't want to turn to hormone replacement or antidepressants to treat their menopause symptoms. Black cohosh is derived from a plant in the buttercup family, and it has been used for centuries. It is taken in many forms like capsules, tablets, or mixed with water. It's thought to behave similarly to serotonin in the brain. This behavior includes easing feelings of depression and regulating body temperature.

Vitamin D

Vitamin D is an essential building block for a healthy body. It promotes healthy bone renewal, normal cell growth, and hormone balance, which are all important for menopausal women. Vitamin D is often referred to as the "sunshine vitamin," as it is produced by the body in response to sun exposure. As women age, the ability to absorb vitamin D decreases, heightening the risk of bone density loss. This makes the need to incorporate vitamin D into the lifestyle and diet. For recommended daily dose of 600 international units (IU), 15- to 20 minute walk is very much beneficial. Apart from this taking a balanced diet containing high vitamin D content foods, such as sardines, tuna, wild salmon, fortified dairy products, and eggs is advisable.

St. John's wort (Choliphulya)

Hypericum perforatum Linn. (family: Hypericaceae) in arabic known as "Ashba berfortum" is perennial herbs/shrubs with yellow flower. It is popularly known as St John's wart. It is found in southern region of Saudi Arabia. The medicinal use of herbs is mentioned in the writing of famous Greco-Arab physicians Istikoglou et al. Avicenna, a famous Arab physician in his book "Canon of medicine" ("Al-Quanoon fil Tib" in Arabic), also described medicinal properties of this herb. The traditional medicinal uses of *H. perforatum* include treatment of jaundice, liver diseases, gall bladder stones, rheumatoid arthritis, and other inflammatory conditions ^[20]. It has become one of the most popular herbs used in the United States, St. John's wort has long been an alternative treatment for menopausal women for alleviating symptoms of mood swings, insomnia, depression and anxiety. Derived from a wild flowering plant called *Hypericum perforatum*, the leaves and flowers are harvested and dried. They can then be brewed in a tea or taken in a pill or liquid form.

Asgand (Indian Ginseng)

Asian Ginseng is a known herb in China, Korea and Native America for as many as five thousand years to treat menopausal symptoms of fatigue, anxiety, and stress. In the same way Indian ginseng (Asgand) works on the endocrine system and helps control the secretion of the hormones. It works wonders on women alleviating stress, preventing menopause-related issues, hormonal imbalances, leading to anxiety, depression, hot flashes and sleeping problems controlling memory loss, and promoting healthy hair and skin. Simultaneously it act as a pain reliever, preventing pain signals from traveling along the central nervous system. Recent research studies have shown anti-inflammatory properties in Ashwagandha (Asgand) by which it has been effective in treating many forms of arthritis.

Turmeric (ChobZard)

Turmeric (Haldi) contains a chemical called curcumin, which might act like the hormone estrogen.¹²

Flax Seeds (Habb ullas)

Flax seeds are one of the richest sources of estrogen, and they top the list of foods having phytoestrogen.

Table 1: Apart from these they are variety of drugs which are used in treating the disease. Some of them are given below

Unani Drugs	Indications	Chemical constituents
<i>Apium graveolens</i> (Karafs)	Liver and spleen disorders, jaundice, rheumatism, gout, and inflammatory diseases	Limonene, p-dimethyl styrene, n-pertyl benzene, caryophyllene, a-selinene, n- butyl phthalide, and sedanenolide
<i>Commiphora opobalsamum</i> (Balsan)	Stomach, jaundice, liver diseases, joint pain, and inflammatory disorders	Flavonoids, saponins, volatile oil, sterol, and/or triterpenes
<i>Hypericum perforatum</i> (Choli phulya)	Jaundice, liver diseases, gall bladder stones, rheumatoid arthritis, and inflammatory conditions	Rutin, hypericin, pseudohypericin, hyperforin, adhyperforin, quercetin, hyperoside, campferol, myricetin, kielcorin, and norathyriol
<i>Moringa oleifera</i> (seedoil) (Sahajna)	Liver disease, lipid disorders, arthritis, and inflammatory disorders	β -carotene, protein, and vitamin c
<i>Nigella sativa</i> (Kalonji)	Liver tonics, digestive, anti-inflammatory, immunostimulant, and remedy for jaundice	Thymoquinone, thymohydro quinone, dithymoquinone, p-cymene, carvacrol, and 4-terpineol
<i>Portulaca oleracea</i> (Khurfa)	Liver disorders, gastrointestinal and inflammatory disorders	Omega-3 fatty acids, alpha-linolenic acid, and vitamins a, b, and c
<i>Solanum nigrum</i> (Makoh)	Liver disorders, inflammatory disorders, rheumatism and swollen joints	Glycoalkaloids, glycoproteins, polysaccharides, gallic acid, catechin, rutin, naringenin, etc.
<i>Tephrosia purpurea</i> (Sarpuka)	Jaundice, liver, biliary and splenic disease, and inflammatory disorders	β -sitosterol, quercetin, lupeol, rutin, delphinidin chloride, cyanidin chloride, isolonchocarpin, lanceolatin a and b, pongamol, karangin, kangone
<i>Curcuma longa</i> (Turmeric)	Loss of appetite, jaundice, liver problems, gall bladder disorders, and arthritis	Curcumin, demethoxycurcumin, and bis- demethoxycurcumin
<i>Ficus carica</i> (Fig)	Liver disease, stomach ailments, digestive problems, obesity, and inflammatory diseases	Psoralen, mucilages, flavonoids, vitamins, nicotinic acid, tyrosine, fucosin, bergaptene, stigmasterol, taraxasterol, beta-sitosterol, rutin, and sapogenin

Compound Drugs

For *Tanqiae madda*: Hab Muntin, Hab Sheetraj, Hab Suranjan, Majoon Suranjan are used in murakkab drugs.

For *Tadeel Mizaj* and to Prevent *Madda* from Coming into the Joints: Majoon Hurmas or Tiryaqe Kabir are used.

Ilaj Bid Tadbeer (Regimenaltherapy)

Munziz Mushil therapy to cleanse the body from morbid matter is the most beneficial. According to Unani System of Medicine, the therapeutic program is planned after identification of the humour (khilt), which is most likely liable for the disease. In most of the cases of gout, the causative humour is phlegm (balgham), melancholic (Sauda) or any other humour and hence adopted treatment is removal of excessive phlegm or the corresponding dominant humour from the particular joints and body in general. Various drugs which are purgative of phlegm (Mushil-e-balgham) or Sauda (Mushil e Sauda) are used after proper coction (Nuzj) of the their humour. Sinne yas (Menopause) has dominance of sauda so Munjiz and Mus'hil Sauda drugs are highly beneficial when added for the treatment.

Hijama therapy has analgesic and anti inflammatory effect thereby proving to be beneficial in various inflammatory joint disorder like gout. It helps to align the blood flow of skin and remove impure blood containing causative pathological substances (the morbid humor) from the diseased part^[30]. Its said in Al- qanoon that Hijamah is also indicated and beneficial in obesity. Obesity which is often predominant in menopausal women would find great results with the Hijama therapy. *Hammam-e-Yabis* (Steam bath) has been proven to be very useful for gouty patients. *Fasd* of Rag e safin is also indicated in Gouty Arthritis.

Nutool with matbookh (Decoction) and zimad are beneficial local application therapy in gout. And last but not the least Exercise: According to Unani literature, etiological factors of Nigris include excessive eating, sedentary life style, lack of exercise so Exercise or rather RIYAZAT is a must for joint flexibility and healthy life. Motadil Riyazat (moderate exercise) is advised regularly for elderly people. Motadil

Riyazat has the capability to produce musakkhin effect in the body and it also expels out harmful substances from the body, enhances the immunity.²⁶ Continual evidence supports the notion that exercise and yoga can help relieve irritability and depression brought on by menopause. Women report that yoga relaxation and stretching techniques help stabilize their moods while improving their overall well-being.

Conclusion

The toxins produced in the disease directly or through oxidative stress mechanism may trigger inflammatory response, which is evident from a significant increase in the proinflammatory cytokines including TNF α and IL6 and inflammation. Majority of the drugs listed have been shown to suppress oxidative stress and are anti inflammatory, apart from being hepatoprotective. This is the asset of Unani Medicine, as according to Hakeem Kabeeruddin, gout is a disease related to hepatic and tissue metabolism (hazm-e-kabidi). Medicinal plants used in unani traditional medicine are rich sources of medicinally active chemical constituents such as phenols, coumarins, lignans, terpenoids, carotenoids, glycosides, flavonoids, organic acids, alkaloids, and xanthene. Some of the purified phytochemicals isolated from these plants have also been shown to possess potent hepatoprotective activity apart from their anti inflammatory, anti oxidant and immunostimulant properties. This system is a boon to mankind if they have the capability to understand it.

Overall, because a wide variety of treatment options are available in Unani medicine to prevent and reverse the negative effects of oxidative stress, inflammatory actions in gout disease associated with reproductive aging, the specific treatment selected should be chosen based on the history and clinical presentation of the patient.

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