Review article

Ameliorating Role Exerted by Al-Hijamah in Autoimmune Diseases: Effect on Serum Autoantibodies and Inflammatory Mediators

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Abstract

Autoimmune diseases have common properties characterized by abnormal blood chemistry with high serum autoimmune antibodies, and inflammatory mediators. Those causative pathological substances (CPS) cannot be excreted by physiological mechanisms. Current treatments for autoimmune diseases involve steroids, cytotoxic drugs, plasmapheresis and monoclonal antibodies. Wet cupping therapy (WCT) of prophetic medicine is called Al-hijamah that treats numerous diseases having different etiology and pathogenesis via a pressure-dependent and size-dependent non-specific filtration then excretion of CPS causing clearance of blood and interstitial fluids. Al-hijamah clears blood passing through the fenestrated skin capillaries. Medical bases of Al-hijamah were reported in the evidence-based Taibah mechanism (Taibah theory). Al-hijamah was reported to be an excellent treatment for rheumatoid arthritis that improved patients' blood chemistry and induced significant clinical improvement and pharmacological potentiation. Al-hijamah improved the natural immunity and suppressed the pathological immunity through decreasing the serum level of autoantibodies, inflammatory mediators, and serum ferritin (a key player in autoimmunity). Al-hijamah reduced significantly pain severity, number of swollen joints and disease activity with no significant side effects. Main steps of Al-hijamah are skin suction (cupping), scarification (sharatmihjam in Arabic) and second suction (triple S technique) that is better therapeutically than the traditional WCT (double S technique). Whenever an excess noxious substance is to be removed from patients' blood and interstitial fluids, Al-hijamah is indicated.Shartatmihjam is a curative treatment in prophetic teachings according to the prophetic hadeeth: "Cure is in three: in shartatmihjam, oral honey and cauterization. I do not recommend my nation to cauterize".Al-hijamah may have better therapeutic benefits than plasmapheresis. Al-hijamah may be promising in treating autoimmune diseases as a sole treatment or adjuvant treatment.

Key words:
Autoimmune diseases, Al-hijamah, Prophetic medicine, Serum ferritin, Rheumatoid arthritis and Plasmapheresis.

List of abbreviations

CPS	Causative pathological substances
DS-DNA	Double-stranded DNA
IC	Immune complexes
Ig	Immunoglobulin
MHC	Major Histocompatibility Complex
NK cells	Natural killer cells
RA	Rheumatoid arthritis
RBCs	Red blood cells
SLE	Systemic lupus erythematosus
TNF	Tumor necrosis factor
WBCs	White blood cells
WCT	Wet cupping therapy

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Introduction

The mere presence of autoantibodies is sufficient to establish the diagnosis of autoimmune diseases, which requires more clinical and additional laboratory evaluation. [1-3]

In general, B-cell stimulation is dependent upon help gained from T cells. Multiple mechanisms exist to regulate the function of self-recognizing T lymphocytes including peripheral deletion mechanisms, induction of anergy and active suppression of self-reacting lymphocytes. Immunopathology of autoimmune diseases involves participation of autoantibodies, complement activation and disorders related to cell-mediated and humoral immunity. [4]

Autoimmune diseases are characterized by an abnormal blood chemistry in which there are high serum levels of auto-antibodies, immune complexes, inflammatory mediators, inflammatory cytokines, soluble cytokine receptors, prostaglandins and others.[4] There is no physiological mechanism to clear serum and/or interstitial fluids from these abnormal constituents. Also, there is no pharmacological treatment to restore the normal blood chemistry or homeostasis through excretion of the above-mentioned pathological substances. Current pharmacological treatments of autoimmune diseases may suppress the inflammatory and autoimmune reactions but do not clear patient's serum or interstitial fluids from the above-mentioned causative pathological substances (CPS). Such pharmacological treatments include steroids,[5] potent anti-inflammatory drugs, cytotoxic drugs,[6] disease-modifying anti-rheumatic drugs[7] and monoclonal antibodies directed against target cells or autoimmune antibodies.[8] Numerous drug side effects are encountered in pharmacological treatments used for treating autoimmune diseases e.g. non-steroidal anti-inflammatory drugs induce gastritis, gastric ulcers and toxicities at high doses, while prolonged steroid therapy causes osteoporosis, hypertension, steroid diabetes, gastric ulcers and steroid dependence.[5]Cytotoxic drugs have many unavoidable serious side effects, which may necessitate drug discontinuation.[6, 9]

Non-specific immuno-suppression may help in treatment of all autoimmune disorders, but adverse side-effects (acquired immunodeficiency diseases, cancer and drug toxicity) can harm the patients rather than benefiting them.[4, 10]

Autoimmune diseases may be organ specific (e.g. Hashimoto's thyroiditis), a mixture of organ specific and systemic symptoms (e.g. rheumatoid arthritis, RA) or diseases with non-organ specific autoimmune reactivity (e.g. systemic lupus erythematosus, SLE).[3, 4]

Al-hijamah (cupping therapy of prophetic medicine) is a well-known treatment modality in the Arabic medical literature in Arabic countries as it is a highly recommended treatment in prophetic medicine.[11-12]

In this article, we will review here important aspects regarding autoimmune diseases, Al-hijamah as a promising treatment, scientific bases beyond Al-hijamah and therapeutic roles of Al-hijamah in treating autoimmune diseases that may be an adjuvant treatment to current treatment modalities for treating autoimmune diseases.[12]

Immunological tolerance (table 1):

The autoreactive B and T-lymphocytes that are sensitized against self-antigens are key players in the pathogenesis of autoimmunity. Immunological tolerance refers to immunological unresponsiveness towards one's own self antigens. It is also called autotolerance and is regulated through many immunological mechanisms in both B and T lymphocytes that prevent them from attacking self-antigens.[1-4]Loss of self-tolerance leads to autoimmunity. Mechanisms for tolerance induction include deletion of autoreactive T-lymphocytes (activation-induced cell death), suppression and deletion of autoreactive B-lymphocytes in the bone marrow, lack of T-cell help for B-cell activation, removal of necessary signals for induction of autoreactivity, absence of appropriate major histocompatibility complex (MHC) molecules for antigen presentation and absence of co-stimulatory molecules.[3-4, 13-14]

Causes of autoimmunity (table 1):

Causes of autoimmunity are wide and diverse. Autoimmunity occurs upon lack of immunological tolerance leading to attack of self-antigens by the own immune system. Autoimmunity has a familial predisposition and is enhanced with infectious microbes producing peptide antigens similar in structure to self-antigens (molecular mimicry), where bacterial peptides cross-react with self-

antigens leading to activation of the immune system. [15]

Moreover, drugs, chemicals bacterial infections and viral infections may cause alteration of self-antigens e.g. tissue proteins, which may affect the behavior of the immune system towards these tissue proteins. Infection with streptococci may cause cross-reactivity of the immune system towards self-antigens where an immunological reaction occurs against the protein of the heart valves resulting in the pathogenesis of rheumatic fever.[16] Similar to that is the appearance of new antigens that are similar to tissue antigens by the effect of viral infections or chemical substances[16]leading to self-attack by one's immunological system[3, 13, 17] e.g. short amino acid sequences in myelin basic protein are identical to sequences in an adenovirus (type-2) protein, while other sequences are homologous to sequences in hepatitis B protein. Altered antigen presentation refers to the presentation of antigens together with MHC by cells not normally expressing MHC.[4, 18-20] This may participate in induction of autoimmunity.

It is noteworthy that defects in the normal regulation of lymphocyte development and activation e.g. defects predisposing to low regulatory T-helper-2, cytokine production and lack of induction of apoptosis to autoreactive T-cell clones "bystanders" during normal immunological responses to infection may break the immunological tolerance leading to autoimmunity.[4, 21]

Etiology of autoimmune diseases includes also genetic defects leading to defects in lymphocyte regulation, loss of stimuli causing apoptosis, development of antigen-related mechanisms and effects of some hormones.[22-23] The ratio of females to males presenting with Hashimoto's thyroiditis is 50:1 and 10:1 in SLE, while the male to female ratio is 9:1 in ankylosing spondylitis.[3-4, 24]
Superantigen-related mechanisms may cause autoimmunity i.e. superantigens activate entire sets of T cells whose T-cell receptors share a common variable region segment. This occurs typically in the T-cell receptor-β chain leading to sensitization of T cells (table 1).[9, 25]

Antigen-related mechanisms include molecular mimicry following infection, cross reactivity with microbial antigens, release of previously sequestered antigens (e.g. during surgery, crystalline lens becomes in contact with the immune system, which may form autoimmune antibodies against it) and altered antigen-presentation by non-professional antigen presenting cells.[26-28]

Table 1. Autoimmunity and immunological tolerance

Autoimmunity
- Results from loss of autotolerance.
- Has several mechanisms:
1. Genetic defects e.g. in HLA alleles and cellular self-antigens.
2. Loss of apoptotic stimuli causing increased proliferation of activated clones of autoreactive cells in the immune system.
3. Superantigen-related mechanisms causing increased proliferation of activated clones of autoreactive T cells in the immune system.
4. Antigen-related mechanisms:
-Molecular mimcry (similarities between self-antigens and foreign antigens)
-Cross-reaction (between self-antigens and foreign antigens)
-Altered antigen presentation (causes a change in immunity against self-antigens)
-Loss of sequsestration (some antigens become in contact with the immune system e.g. eye lens)
Immunological tolerance
(Protects against development of autoimmune diseases)
A. Central tolerance
1. In the thymus
-Termed negative autoselection
-Involves deletion of autoreactive T-cells
-Occurs when T-cell receptors mistakenly bind to self-antigens and become autoreactive.

2. In the bone marrow
-Termed negative autoselection
-Involves deletion of autoreactive B-cells
-Occurs when immature B-cell receptors mistakenly bind to self-antigens and become autoreactive.

B. Peripheral tolerance

- Occurs outside the thymus and bone marrow
-Autoreactive cells become inactivated through several mechanisms as:
-Absence of appropriate MHC molecules
-Lack of co-stimulatory molecules
-Lack of T-cell help for B-cells activation
-Active suppression of autoreactive cells (mediated by T-cells).

Immunologic mechanisms of tissue damage in autoimmune diseases:

Immunological mechanisms beyond tissue damage occurring in autoimmune diseases include three different types of hypersensitivity reactions that are type II, III and IV. In type II hypersensitivity reactions that are called cytotoxic or cytolytic inflammatory reactions, autoantibodies (IgG or IgM) attack surface the antigens present on the outer surface of body cells causing cell lysis. Type II hypersensitivity reactions causes activation of the complement (a group of sequential proteins activated during immunological conditions) and opsonization (opsonin-enhanced phagocytosis by neutrophils, natural killer cells and macrophages). There is also antibody-mediated phagocytosis. Examples include Grave's disease, autoimmune hemolytic anemia, pernicious anemia (antibodies block the function of important proteins e.g. intrinsic factor necessary for vitamin B12 absorption), Goodpasture's disease, Idiopathic thrombocytopenic purpura, SLE, Hashimoto's thyroiditis, nephrotoxic nephritis and myasthenia gravis.[13, 29]

In type III-induced autoimmunity (immune complex-mediated reactions), antigens and autoantibodies exist and escape from removal by the reticuloendothelial cells. This leads to complement activation, mast cell degranulation, histamine secretion and platelet aggregation (microthrombi formation). Examples of type III-induced autoimmunity include SLE and rheumatoid arthritis (RA). Treatment of type III-induced autoimmunity may include the excretion of autoantibodies and immune complexes through plasmapheresis.[1-4, 13]

In type IV-induced autoimmunity (delayed type hypersensitivity reactions), tissue damage occurs as a consequence of sensitized T lymphocyte activation leading to macrophage and lymphocytes activation with production of hydrolytic enzymes, reactive oxygen species, nitric oxide and cytokines e.g. tumor necrosis factor (TNF), interleukin-1 (Il-1) and Il-6. Insulin-dependent diabetes mellitus may belong to this category of diseases.[13, 26]

Diagnosis of autoimmune diseases:

As there is a large number of autoantigens activating the own immune system resulting in the formation of autoantibodies by the non-tolerant self-reacting B cells, diagnosis of autoimmune diseases vary from disease to disease according to the organ involved and pathogenesis. However, there are common criteria for the laboratory diagnosis of autoimmune diseases, which include high serum immunoglobulins, high serum autoantibodies (e.g. anti-nuclear, anti-mitochondrial, anti-smooth muscle and rheumatoid factor in RA), high serum immune complexes, high serum tissue-specific autoantibodies (e.g. anti-thyroid antibodies), high serum soluble cytokine receptor (e.g. soluble IL-2R in RA) and low serum complement.[1-4, 13]

Current treatment modalities for autoimmune diseases:

Current treatment for autoimmune diseases is directed towards treating the 3Cs (cause, condition and complications) with limited

success in some cases. Pharmacological treatment involves anti-inflammatory agents e.g. steroids[5] and non-steroidal anti-inflammatory drugs to decrease the inflammatory reaction and to lower the production of inflammatory mediators upon immunological attack by the own immune system. Cytotoxic and immunosuppressive drugs may be helpful to decrease the activity of the immune cells e.g. methotrexate.[9]Cytokine inhibitors e.g. anti-TNF may lower the pathological effects exerted by the excess pathological TNF cytokines.[30] Monoclonal antibodies are directed therapeutically to bind to inflammatory cytokines[31] e.g. infliximab binds to TNF when treating RA.[32] However, therapeutic monoclonal antibodies are so expensive and carry numerous serious side effects. [13, 34]

Al-hijamah (wet cupping therapy of prophetic medicine) clears blood from CPS

Histologically, ultrastructure of the skin (as evidenced by electron microscopic studies) is formed of three layers: epidermis, dermis and hypodermis**(Fig. 1A-B)**. Epidermis is the outermost superficial layer that contains no blood capillaries. Uppermost layer of the epidermis is a layer of non-viable cells, the keratinized epithelium layer (stratum corneum = horny cell layer) that constitutes the skin barrier (having an average thickness of 10–20 μm) whose main function is to provide the primary barrier for the percutaneous absorption or excretion of substances and water across the skin. Underlying the stratum corneum is the viable epidermis (50–100 μm thick), that is responsible for the regeneration of the stratum corneum.[35]

The dermis (1–2 mm thick) is the second cell layer of the skin that is directly adjacent to the epidermis and provides the mechanical support for the skin. The fenestrated skin capillaries lie at the dermo-epidermal junction.[35]Those superficial fenestrated capillary networks[36-38] are suitable for the function of pressure-dependent filtration upon application of negative suction pressure as that done during Al-hijamah.

Practically, when performing Al-hijamah, skin scarifications (small superficial incisions, shartatmihjam in Arabic) done during Al-hijamah should be so superficial (about 0.1 mm in depth) just to open the skin barrier and reach the superficial fenestrated dermal capillaries. No need to scarify the skin deeply during Al-hijamah in order not to damage the fenestrated dermal capillaries (causing loss of capillary fenestrations and filtration function) or cause unnecessary enormous bleeding. [39]

The term wet cupping therapy (WCT) includes both Chinese (traditional) WCT and Al-hijamah (WCT of prophetic medicine). Al-hijamah has solid scientific and medical bases through clearing both the blood and interstitial fluids from CPS through a percutaneous pressure-dependent filtration of the blood passing through the fenestrated skin capillaries **(Fig. 1A-B)**.[11-12] Traditional WCT has two main steps: scarification of the intact skin (not preceded by cupping) and suction using sucking cups applied to the skin surface i.e. double S technique. Al-hijamah has three main steps: 1st suction step using sucking cups applied to the intact skin (not preceded by a cupping step) to create skin upliftings, scarification of the skin uplifting (shartatmihjam) and a 2nd suction step i.e. triple S technique. This is immediately followed by pressure-dependent excretion of the CPS through the shartatmihjam according to the evidence-based Taibah mechanism (Taibah theory)[11-12] suggested recently by Salah M. El-Sayed. Taibah mechanism states that Al-hijamah is a minor surgical excretory therapeutic procedure than can clear both the interstitial spaces and blood partially from noxious substances causing the disease etiology or resulting during disease pathogenesis. This occurs through making use of the skin histological structure where the fenestrated skin capillaries may act as filters upon application of suction pressure produced inside the sucking cups during Al-hijamah.[11-12]This may facilitate regaining physiological homeostasis and recovery to variable extents depending on the degree of clearance of noxious substances, proper practice of Al-hijamah at relevant anatomical sites and on the other therapeutic benefits that can be gained during disease treatment using Al-hijamah.[12] Scientific principles of Al-hijamah are similar to the principle of abscess evacuation where compression pressure on the abscess walls from outside evacuates pus (noxious substances in Al-hijamah) through the created abscess openings (represented by skin scarifications in Al-hijamah).[12] Medical bases

of Al-hijamah are similar in principle to renal glomerular filtration where the pressure difference between the hydrostatic capillary pressure and Bowman's capsule (represented by the pressure difference between sucking cups and skin capillaries during Al-hijamah) helps pressure-dependent filtration of the skin blood capillaries. Al-hijamah is a three-step technique[40-41](skin suction, scarification and suction), which includes all steps of both Chinese dry cupping therapy (a single suction step) and Chinese WCT (skin scarification followed by suction).[11-12] CPS include both substances causing the disease process and substances resulting during disease pathogenesis.[11-12] CPS in autoimmune diseases include autoantibodies, antigen-antibody complexes, inflammatory mediators, prostaglandins, inflammatory cytokines, soluble cytokine receptors, hydrolytic enzymes, ROS and others **(Fig. 2)**.[1-4]

Figure 1A **Figure 1B**

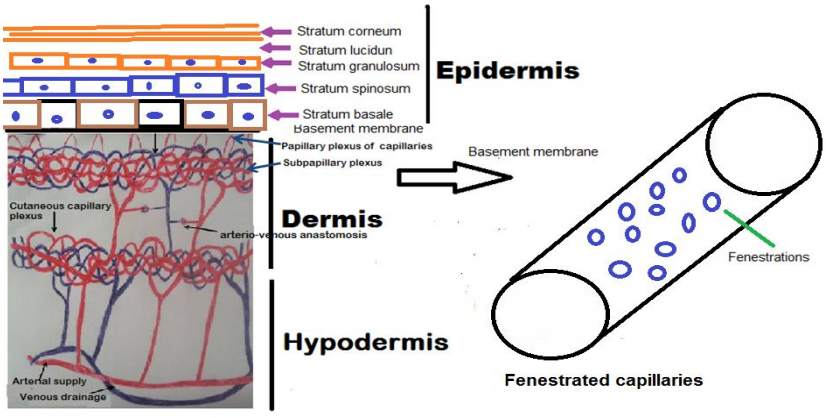


Figure 1. Electron microscopic structure of dermal vasculature.
A.skin has a superficial network of fenestrated dermal capillaries.
B. Dermal fenestrated capillaries have pores that suit the function of pressure-dependent filtration during Al-hijamah.

Figure 2

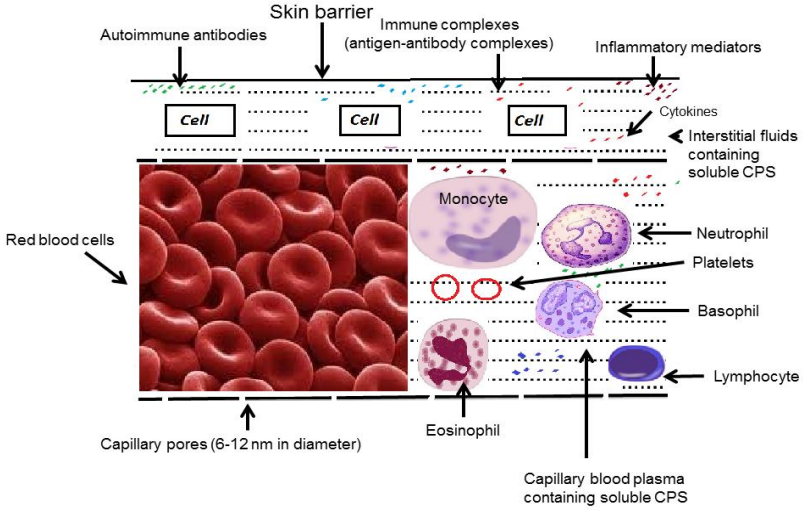


Figure 2.Causative pathological substances (CPS) of autoimmune diseasesare present in serum and interstitial fluids. CPS can be filtered through capillary pores then excreted out through the pressure-dependent effect of Al-hijamah.

The first and the last steps in Al-hijamah are sterilization of skin in a totally aseptic atmosphere. WCT of prophetic medicine (Al-hijamah) exerts three main functions in its three main steps: cupping (suction of skin inside cups) creates skin upliftings (skin dome) that collect interstitial fluid and filtered fluid containing CPS **(Fig. 3A-C)**, puncturing (scarifying skin to excrete collected fluids) and cupping (second suction) introduces a negative pressure through the induced skin scarifications for filtration of capillary blood from CPS) **(Fig. 4A-C)**.[11-12] Cupped blood is the bloody excretion inside sucking cups that includes excreted disease CPS **(Fig. 5, 6A-C)**. Each suction step is a pressure-dependent filtration step for clearing blood and interstitial spaces from disease CPS in a non-specific size-dependent manner.[11-12] Steps of Al-hijamah include two suction steps (two pressure-dependent filtration steps); while traditional WCT includes a single suction step (a single filtration step). For that, Al-hijamah is therapeutically better than traditional WCT for the better blood clearance during Al-hijamah and for many other causes as previously reported.
[11-12, 42]

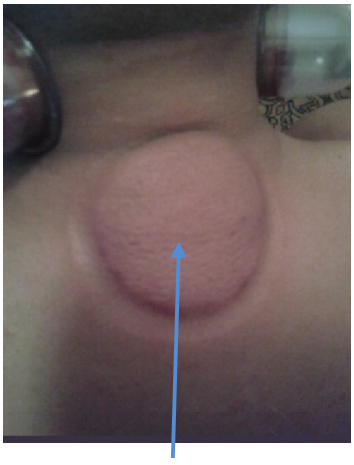


Figure 3A. Skin uplifting (dome) created after putting sucking cup in the kahel region

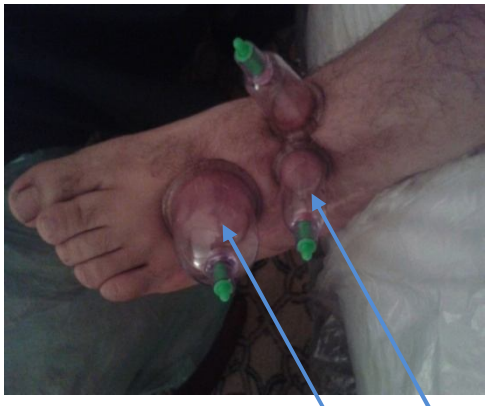


Figure 3B. Skin uplifting (dome) created inside sucking cup put at local regions of pathology in the foot

Figure 3C

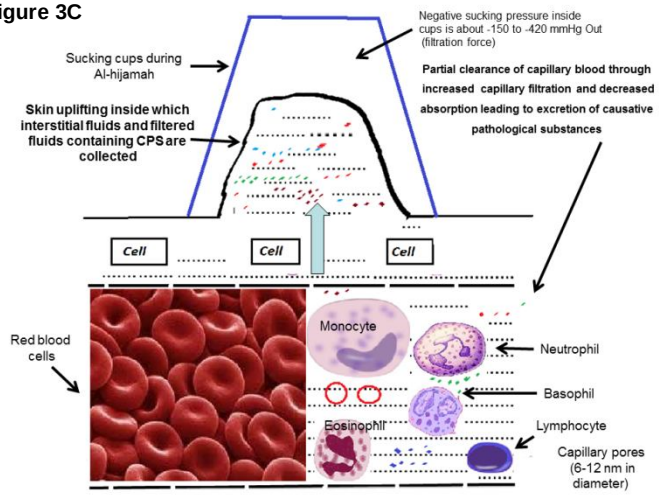


Figure 3. Wet cupping therapy of prophetic medicine (Al-hijamah) for treating autoimmune diseases.

A. First step in Al-hijamah is 1st suction step using sucking cups. Skin uplifting (dome) starts to form and progressively increases in size due to the viscoelastic nature of the skin under the effect of negative pressure suctioning.

B. A similar skin uplifting is created through putting sucking cups at the dorsum of the foot (local painful and inflammatory sites).

C. Boyle's law (pressure is inversely related to volume) is applied here. Collected fluids inside skin uplifting contain collected interstitial fluids with CPS (autoimmune antibodies, immune complexes, inflammatory mediators and cytokines).

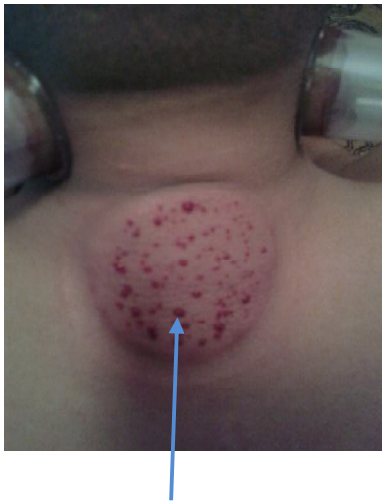


Figure 4A.(Skin scarification = shartatmihjam in Arabic). ***Criteria of shartatmihjaminclude:****Superficial longitudinal small incisions that must be confined to the skin upliftings and preceded by 1st suction step. Shartatmihjam should be superficial (0.1-0.2 mm in depth), short (1-2 mm in length), multiple and evenly distributed.*
- Sucking cups should be applied immediately after scarifying the skin upliftings. Shartatmihjam is induced here in the dorsal surface of the kahel region (skin over the 7th cervical vertebra).

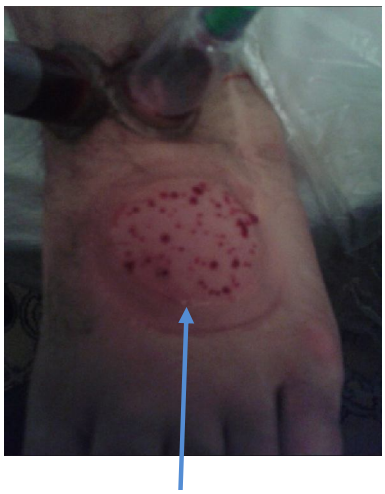


Figure 4B.(Skin scarification = shartatmihjam in Arabic). ***(Skin scarifications of Al-hijamah = shartatmihjam in Arabic).***
Shartatmihjam is done here at local anatomical areas at/ or very near to the site of pathology for the aim of better local tissue clearnce.
- Skin scarifications should be confined to skin upliftings, superficial (0.1-0.2 mm in depth), short (1-2 mm in length), multiple and evenly distributed. Cups should be applied immediately after scarifying skin upliftings.
- Shartatmihjam is induced here in the dorsal surface of the foot region.

Figure 4C

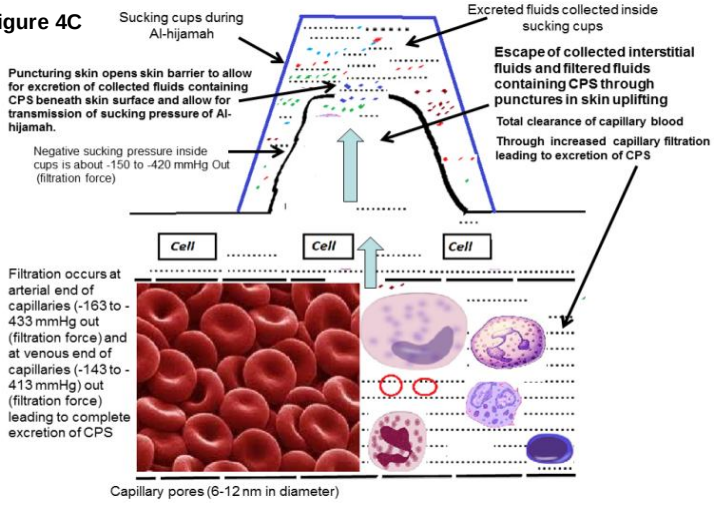


Figure 4. Second step in Al-hijamah is shartatmihjam. Openings of the skin barrier through skin scarifications (shartatmihjam in Arabic) allow the excretion of the collected fluids containing CPS mixed with some blood due to scarification trauma. A. Shartatmihjam was created in the Kahel region.
B.Shartatmihjam was created on the dorsuma of the foot region.
C. detailed pressure-dependent excretion occurring through shartatmihjam.

Indeed, Al-hijamah is more comprehensive than traditional WCT and includes all steps and therapeutic benefits included in traditional WCT and treats all disease conditions treated by traditional WCT. Opposite is not true as traditional WCT is a partial form of Al-hijamah. We previously reported so many therapeutic benefits related to Al-hijamah and explained to what extent that is beneficial in treating so many different disease conditions.[42] This can be explained by knowing that Al-hijamah induces non-specific general blood clearance from noxious substances, immunological enhancement, pharmacological potentiation, analgesic effects, physiotherapy benefits, hemostatic benefits, hematological benefits, hemodynamic benefits, nutritional benefits and others as we previously discussed.[42]All those therapeutic benefits help the restoration of homeostasis and recovery from the disease condition. To our knowledge, there are no reported serious side effects, limitations or absolute contraindications related to the proper practice of Al-hijamah. Therapeutic indications of Al-hijamah were reported previously.[42] In other reports, non-specific blood clearance occurring during Al-hijamah was reported to clear venous blood from ferritin (ng/ml) by about 22%, from LDL-Cholesterol (mg/dl) by about 23%, from triglycerides (mg/dl) by about 27%, from cholesterol (mg/dl) by about 13.7% and from serum uric acid (mg/dl) by about 17%.[43] Blood samples were taken before Al-hijamah and ten days after it,[43] which measured the excretory and blood clearance benefits of Al-hijamah.[43] Recently, we suggested Al-hijamah as a novel promising treatment modality for iron overload conditions e.g. thalassemia.[44] Based on that, Al-hijamah can be regarded as an artificial excretory procedure that opens the skin barrier and enhances the natural excretory functions of the skin[11-12] as evidenced by the report that WCT enhanced the patients' natural immunity via increasing the number of natural killer (NK) cells and inducing leukocytosis.[45] The pressure-dependent filtration and excretion through Al-hijamah is similar in scientific principle to that occurring in the renal glomeruli and to that occurring during the pressure-dependent abscess evacuation where excretion of noxious CPS causes systemic blood clearance and restores physiological homeostasis according to the evidence-based Taibah mechanism.[12]

Pressure-dependent excretion in Al-hijamah versus the renal glomeruli (table 2)

Largemolecules e.g. β-lipoprotein (Low density lipoproteins, LDL) cannot be filtered through the renal glomeruli, as their molecular weight (1,300,000) is too large to be filtered. Metabolism of LDL and other lipoproteins occur naturally inside the human body. However, excess pathological increase in LDL-cholesterol is a risk factor for the development of atherosclerosis and coronary heart diseases.[43] LDL binds to LDL receptor in the hepatocyte surface where an endocytosis process occurs resulting in the formation of endosomes. Then, the endosome fuses with a lysosome carrying hydrolytic lysosomal enzymes that hydrolyze the components of LDL-cholesterol into cholesterol esters, LDL proteins, and other lipids.[46] LDL was reported to be cleared percutaneously during Al-hijamah,[43] which confers therapeutic excretory functions to Al-hijamah that cannot be attained by physiological urinary excretion. However, other large molecules e.g. gamma globulins can pass through the skin capillaries into the interstitial fluid.[47-49] Recently, serum IgE and IL-2 levels significantly decreased in patients having skin dermatoses after Al-hijamah, which confirms their excretion in the cupped blood.[50] Methodology described in this study was the triple S technique (Al-hijamah) not traditional WCT although the authors mistakenly described it as Chinese WCT.[50]

In other words, WCT opens the skin barrier and enhances the natural excretory role of the skin. This may help in excreting abnormally increased gamma-globulins (e.g. rheumatoid factor), which was reported to be decreased significantly in serum of RA patients following Al-hijamah. Interestingly, large-sized macromolecules e.g. β-lipoproteins were reported to pass through the fenestrated pores of the skin capillaries out to the skin interstitial fluids,[47-49] which may facilitate their excretion through Al-hijamah as evidenced by previous studies.[11-12, 47-49]

Excretion through the renal glomeruli is limited to hydrophilic substances while excretion through Al-hijamah includes both hydrophilic and hydrophobic substances e.g.

cholesterol and triglycerides.[43] The excretory pressure gradient utilized during Al-hijamah (-150 - 430 mm Hg) is much higher than the net pressure gradient utilized for filtration at the renal glomeruli (10 mm Hg). Al-hijamah exerts a final excretion into the cupped blood while the glomerular filtrate has to undergo tubular reabsorption and secretion processes before final excretion. Excretion through the renal glomeruli is affected by particle charges of excreted substances and glomerular endothelium while excretion through Al-hijamah is not reported to be affected by that.[11-12]

Recently, Al-hijamah was reported to benefit from the temporary compression pressure exerted on the skin surface by the application of sucking cups for few minutes through the occurrence of reactive hyperemia phenomenon.[11-12] In reactive hyperemia, vascular compression causes a decrease in the blood supply to the skin for few minutes resulting in accumulation of vasodilator metabolites. As soon as vascular compression is removed, blood flow to the skin dramatically increases, which is called hyperemia.[52] This brings more blood to the skin circulation and enhances the clearance of blood from CPS. Moreover, WCT was reported to increase filtration at both capillary ends to clear blood from CPS to restore physiology and homeostasis[11-12]**(Fig. 4-7).**

Table 2. Differences between excretion through Al-hijamah and through renal excretion

	Al-hijamah (11-12, 42, 44, 50, 71)	**Renal excretion**
Excretion	Artificial and short in duration	Natural and continuous
Route	Percutaneous	Urinary
Mechanism	Pressure-dependent and size-dependent filtration through the fenestrated dermal capillaries followed by excretion	Pressure-dependent and size-dependent filtration through the fenestrated glomerular capillaries followed by excretion
Possibility of direct excretion	Possible e.g. excretion of urate crystals at gouty skin regions	Not (urine is processed through tubular reabsorption and secretion before final excretion)
Function	Non-specific biochemical clearance of blood and interstitial fluids. Many other therapeutic benefits	Hematopoietic, excretory and endocrine functions in the kidney
Excretion of hydrophobic substances e.g. cholesterol and triglycerides	occur	Not
Clearance	Blood clearance from both hydrophilic and hydrophobic noxious substances	Blood clearance from hydrophilic metabolic byproducts
Pressure gradient utilized for filtration	150 to 430 mmHg	10 mmHg
Excretory product	Bloody fluid (cupped bloody excretion) that contains mainly old damaged blood cells and CPS	Watery urine (variable in specific gravity and constituents)
Protein excretion	Present	Absent
Immunoglobulin (autoantibody) excretion	Reported	Absent
Excretion of inflammatory mediators	Reported	Absent

Volume of excretion	Variable and depends on pathology e.g. increases in hypertension and tissue edematous swellings	Variable and depends on water balance e.g. increases in hydration states and decreases in dehydration
Shartatmihjam (induced skin scarifications)	Present	Absent
Charge carried by excreted particles e.g. –ve charges in albumin	Does not affect excretion	Affect
Excretion of soluble antigens, soluble cytokine receptor and antigen-antibody complexes	Reported	Not done
Role in regulation of acid-base balance	Less important	Vital (via excretion of various concentrations of titratable acids)
Other therapeutic benefits	Analgesia, physiotherapy, homeostasis and tissue-protective benefits	Hematopoietic, acid-base balance and homeostatic benefits
Role of Al-hijamah	Better clearance of blood and interstitial fluids in healthy subjects	Renal patients benefit from Al-hijamah in improving the defective clearance functions and relieving side effects of hemodialysis.
Other names	Cupping therapy of prophetic medicine, triple S technique	Urine formation and micturition

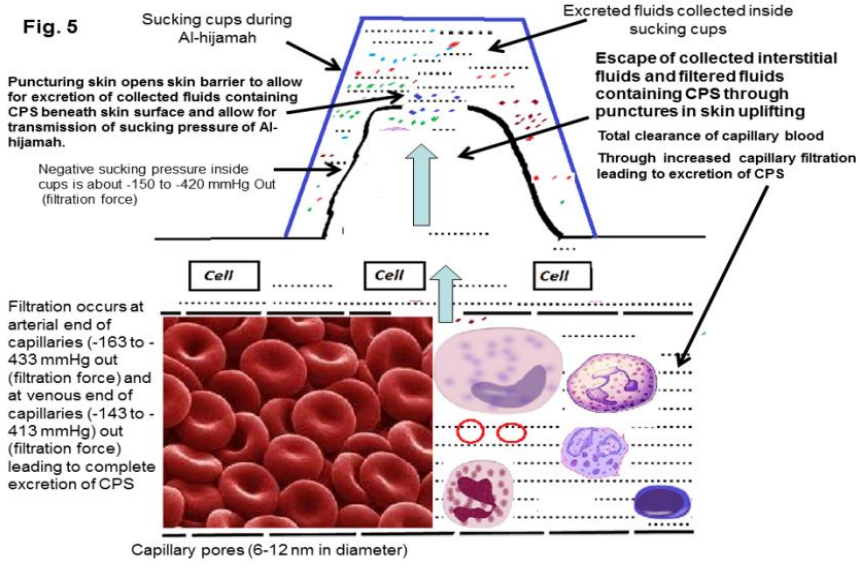
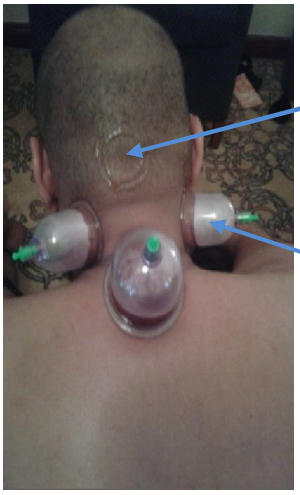


Figure 5. Third step in Al-hijamah is ^{2nd} suction using sucking cups. Excreted cupped blood carries the filtrate mixed with some old hemolyzed and fragmented blood cells. A. Cupped blood excreted at Kahel and Akhdayin regions. B. Cupped blood excreted at local foot region. C. Pressure-dependent excretion of a serous plasma-like fluid.



Local honey may be put for proper fixation of sucking cups

Sucking cups put at akhdayin regions (postero-inferior to ear lobules)

Figure 6A

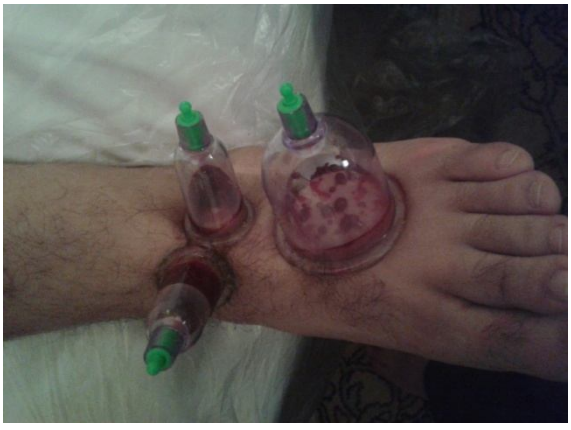
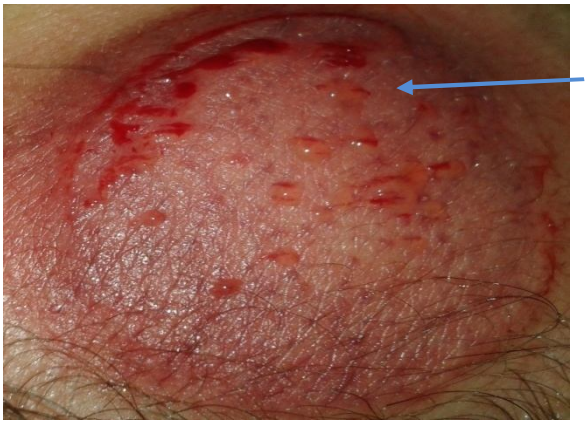


Figure 6B

Figure 6. Third step in Al-hijamah is ^{2nd} suction using sucking cups. Excreted cupped blood carries the filtrate mixed with some old hemolyzed and fragmented blood cells.
A. Cupped blood excreted at Kahel and Akhdayin regions.
B. Cupped blood excreted at local foot region.
C. Pressure-dependent excretion of a serous plasma-like fluid.



Al-hijamah-induced serum filtration. Continuous suction inside sucking cups causes pressure-dependent filtration then excretion of a serous plasma-like fluid.

Figure 6C

Fig. 7

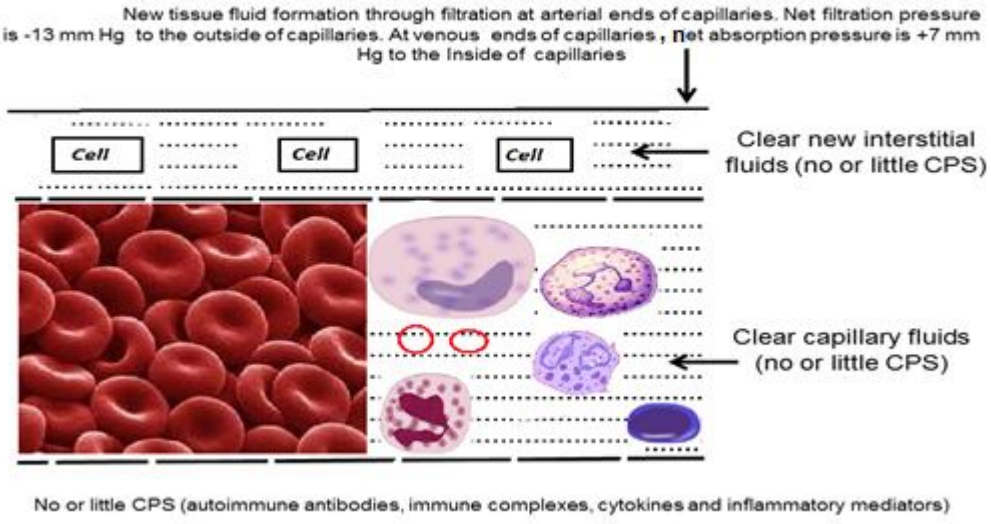


Figure 7. Restoration of physiology and homeostasis. This occurs after pressure-dependent excretion of CPS of autoimmune diseases during Al-hijamah

Al-hijamah as a reported promising treatment for rheumatoid arthritis

In Arabic countries, the scientific terms WCT, blood cupping therapy and bloodletting cupping therapy refer to the triple S technique (Al-hijamah) not the double S technique (traditional WCT) as Al-hijamah is an inherited modality of treatment since the era of prophetic medicine in the Arabic medical literature. Recently, bloodletting cupping therapy was reported to successfully treat autoimmune diseases e.g. RA where the pain of RA was maximally reduced.[45] Interestingly, CPS of RA e.g. rheumatoid factor (RF) and soluble interleukin-2 receptors (SIL-2R) were reduced significantly in patients' venous blood after Al-hijamah, which gave the conclusion that those CPS were excreted in the cupped blood during the pressure-mediated filtration in WCT (Al-hijamah). Interestingly, Al-hijamah was reported to increase the number of NK cells.[45] NK cells are a subset of effector lymphocytes that, in contrast to T cells, do not require prior sensitization with antigen for their immunological function. The lytic functions of NK cells are regulated by a set of inhibitory receptors (killer inhibitory receptors) recognizing MHC class I determinants on target cells.[1-4, 13] Recently, traditional WCT (partial form of Al-hijamah) was reported to clear blood from pain-mediating substances e.g. substance P, which may explain partially the analgesic and antinociceptive effects of Al-hijamah.[54]

Excretion of RF, SIL-2R and other CPS of RA through Al-hijamah[45] constitutes a non-specific serum clearance in those patients that is so beneficial and paves the way for facilitating the therapeutic benefits exerted by pharmacological treatments. When a significant serum clearance is achieved, pharmacological treatments will be directed towards a lower concentration of CPS, which will be easier to manage pharmacologically. Excretion of disease CPS may be better than treating those CPS or abolishing their pathologic effects while they are present inside the human body. [55-56]

Lessons gained from treating RA with Al-hijamah

An interesting single study was done in Al-Azhar university in Cairo, Egypt[45] that evaluated the improvements in rheumatoid

patients treated using a combination of Al-hijamah with conventional pharmacological treatments revealed marked significant improvements in all the tested clinical parameters during the three successive months that followed Al-hijamah in a time-dependent manner. Clinical improvements were progressively increasing month after month. Best improvements were recorded in the 3rd month after performing Al-hijamah**(table 3)**. Visual analog scale (VAS) for measuring pain intensity was reported to decrease by about 59% in the combined treatment group versus 20% in the conventional pharmacological treatment group. Tender joint count (TJC)decreased by about 76% in the combined treatment group versus 34% in the conventional treatment group. Swollen joint count (SJC) decreased by about 78% in the combined treatment group versus 18% in the conventional treatment group. Disease-activity score (DAS) decreased by about 33% in the combined treatment group versus 4% in the conventional treatment group. (45)

As for the laboratory parameters that measured RA activity, there was also a significant improvement in all the tested parameters. SIL-2R (pg/ml) decreased by about 11.55% in the combined treatment group versus 0.64% in the conventional treatment group. Concentration of SIL-2R was reported to correlate with disease activity, clinical deterioration and increased patients suffering.(45)

Erythrocyte sedimentation rate (ESR) (mm/hour) decreased by about 17% in the combined treatment group versus 2.3% in the conventional treatment group. C-reactive protein (CRP) (mg/dl) decreased by about 79.3% in the combined treatment group versus 11.4% in the conventional treatment group. RF (IU/ml) decreased by about 85.54% in the combined treatment group versus 29.75% in the conventional treatment group.(45)

As for the laboratory parameters measuring the natural immunity, there was a significant improvement in all the tested parameters. Physiological leukocytosis was evident where leukocytes count ($x10^9$) increased by about 44.81% in the combined treatment group versus a decrease of about 3.6% (leucopenia) in the conventional treatment group. Percentage of NK cells (NK Cell %) increased by about 33.29% in the combined treatment group versus 1.17% in the conventional treatment group.(45) Based on that, Al-hijamah enhanced the natural innate immunity and suppressed the pathological immunity (autoantibodies, inflammatory cytokines production and immune pathology-related inflammatory reactions).

As for the pharmacological potentiation effects, they measured the percentage ratio of therapeutic effects of a combination of Al-hijamah with conventional treatment (e.g. for RA) versus the conventional treatment group (i.e. % improvement after combined treatment / % improvement after conventional treatment). All the measured parameters of pharmacological potentiation were significant. Using the values in table 3, calculated therapeutic beneficial effects improved after combined treatment (versus conventional treatment only) by 2.95 folds for VAS, by 2.235 folds for TJC, by 4.333 folds for SJC, by 8.25 folds for DAS, by 18.04 folds for SIL-2R, by 7.39 folds for ESR, 6.95 folds for CRP, by 2.87 folds for RF, by 12.44 folds for percentage increase in leucocytes (leukocytosis) and by 28.45 folds for percentage increase in NK cells.(45) This confirms the evidence-based Taibah mechanism (Taibah theory for scientific mechanisms and rationale of Al-hijamah)(11-12) where Al-hijamah exerts synergistic effects with pharmacological treatments when treating RA.(45) As Al-hijamah is a mechanical (not a pharmacological) line of treatment, no chemical interaction or pharmacological antagonism will occur when combining Al-hijamah with pharmacological treatments.

However, for further future research studies, it will be better to specify a separate study group to investigate the pure therapeutic effect of Al-hijamah only, which may help in quantitating to what extent is the participation of Al-hijamah as a sole treatment in relieving patients with RA. It is important to mention some technical details during reporting the therapeutic results of Al-hijamah e.g. the best anatomical sites for putting sucking cups for treating RA and the possible therapeutic rationale beyond selecting the joint anatomical sites and the remote anatomical sites. Interestingly, we recently reported the therapeutic rationale beyond selecting local and general anatomical sites for treating many diseases including RA.(57) Briefly, as we had learnt from prophetic medicine, putting sucking

cups at the affected joint sites clears the interstitial fluids of the selected areas from disease CPS while putting sucking cups at the remote anatomical sites from the site of pathology e.g. in the back of the trunk and the back of the neck clears better the serum from CPS.[57] Cumulative clearance of both serum and interstitial fluids (through excretion of noxious substances partially or totally) may help improving disease pathophysiology, restore physiological homeostasis (Fig. 7), and terminate or ameliorate disease pathogenesis which may be reflected positively upon improving the clinical outcome. Putting sucking cups at sites of pathology (e.g. inflammation) helps to clear those sites from substances causing the pathology (e.g. inflammatory mediators).

Moreover, the authors were not successful when they did not estimate the laboratory parameters in the first few hours after Al-hijamah to report on the pure excretory benefit that occurred due to Al-hijamah-induced blood and interstitial fluid clearance.

The improvement that occurred in the clinical condition of RA patients was secondary to the subsidence of the autoimmunity and inflammatory reactions secondary to the decrease in serum parameters of the noxious substances and the physiological increases in serum parameters of WBCs and NK cells. The improvement that was reached in the 3rd month after Al-hijamah is due to the combinatory effect of CPS excretion (immediate therapeutic benefit after Al-hijamah), immunity enhancement (gradually increasing therapeutic benefit) and subsidence of pathology (secondary therapeutic benefit to blood clearance and immunomodulation).

Therapeutic importance of clearing ferritin in autoimmune diseases using Al-hijamah

Ferritin is the circulating iron storage protein that is regarded also as an acute phase reactant marker exhibiting high levels in different inflammatory conditions. Hyperferritinemia was reported in SLE patients, diabetic patients, multiple sclerosis patients, and RA patients. Hyperferritinemia is a marker of disease activity in SLE patients.[58]Compared to subjects with normal ferritin levels, a significantly greater proportion of patients with hyperferritinemia had thrombocytopenia, lupus anticoagulant and anti-cardiolipin antibodies, which may suggest that hyperferritinemia may be an early marker in secondary antiphospholipid syndrome in SLE patients.[59]

Elevation of serum ferritin was documented in patients with juvenile RA and was helpful in monitoring the response to therapy.[60] Ferritin may have a role in the pathogenesis of autoimmune diseases e.g. the antiphospholipid syndrome. Hyperferritinemia was reported to be correlated with the antiphospholipid syndrome, its catastrophic variant and the presence of anti-CMV antibodies among those patients.[61] Moreover, hyperferritinemia (≥1,250 µg/L) was reported to rule out some autoimmune diseases and hematologic diseases[62] where increased serum ferritin and reduced activity of iron-regulatory proteins were reported to indicate monocyte iron accumulation, which may be important for the pathophysiology of anemia of chronic diseases in humans.[63] Moreover, increased serum iron and ferritin constitute the hallmark of iron overload conditions as thalassemia, sideroblastic anemia and hemochromatosis.[42, 44]

Furthermore, hyperferritinemia (≥2,500 µg/L) was reported to be associated with the relapsing-progressive type of multiple sclerosis,[64] adult-onset Still's disease,[65] primary and secondary hemophagocyticlymphohistiocytosis.[66-67] Interestingly, low serum ferritin was reported to be associated with a good response to therapy in patients with autoimmune disease-associated hemophagocytic syndrome[66-67] that usually presents with hyperferritinemia (> 500 µg/L), high fever, hepatosplenomegaly, lymphadenopathy, central nervous system involvement and disseminated intravascular coagulation.[68]

Based on that, significant clearance of serum ferritin in patients having autoimmune diseases using Al-hijamah is so beneficial in correcting the pathogenesis in such patients and in restoring physiological homeostasis (Fig. 7).

Al-hijamah versus phlebotomy and plasmapheresis Therapeutic benefits and improvements reported after Al-hijamah were better than those reported after phlebotomy[69-71] where Al-hijamah improved much better the arterial O_2 saturation and respiration when treating smoking in patients having chronic

obstructive pulmonary diseases without causing significant blood loss.[69] Al-hijamah was reported to do better than phlebotomy in decreasing CRP dramatically and improving the ESR in patients having chronic urticaria and angioedema. [70] Methodology described in those studies was the triple S technique (Al-hijamah) not traditional WCT. Detailed differences between Al-hijamah and phlebotomy were previously reported.[44, 71]
Autoimmune diseases (including RA) exhibit a similar abnormality in blood chemistry as in RA i.e. they have high serum level of autoimmune antibodies and immune complexes **(tables 3-4)**. Plasmapheresis (plasma exchange transfusion) is used for treating some autoimmune diseases to clear blood plasma from autoimmune antibodies.[72-74]Plasmapheresis aims at removing immune mediators as autoantibodies, immune complexes, and proinflammatory substances e.g. complement components and coagulation factors.[72-74]Diseases treated by plasmapheresis include Goodpasture'sdisease (in which antiglomerular basement membrane antibodies are present), SLE, myasthenia gravis and Guillain-Barre syndrome. Plasmapheresis is an expensive, risky, sophisticated, time-consuming (1-3 hours) excretory treatment that needs a special plasmapheresis machine. Preparatory steps for plasmapheresis include assessing hematological indices and plasma volume. Steps of plasmapheresis include separating plasma from blood cells and discarding plasma. Replacement fluid should be given to patients, which may include albumin, electrolyte solutions, hydroxy-ethyl starch, and fresh frozen plasma or purified protein products such as individual clotting factors or antithrombin III.[72-74] Massive sudden removal of antibodies during plasmapheresis may lead to a rebound increase in the production of autoantibodies. [74]So, plasmapheresis should be done under the umbrella of immunosuppressive therapy to decrease the possibility of rebound increase in autoantibodies[75-76]**(table 5).**

Table 3. Therapeutic improvements after Al-hijamah in treating RA reported by Sahbaa et al.[45]

	Before Al-hijamah	**3 Months after conventional treatment only**	**3 Months after combined conventional treatments + Al-hijamah**
Clinical parameters			
Visual analog score (VAS)	7.80±0.28	6.25±1.33	3.20 ±1.54
Tender joint count (TJC)	19.53±0.95	12.8±54.01	4.73 ± 2.76
Swollen joint count (SJC)	15.83±0.97	12.95±3.66	3.56 ± 1.99
Disease-activity score (DAS)	6.15±0.10	5.92±0.61	4.10 ± 0.69
Laboratory parameters			
Soluble interleukin-2 receptors SIL-2R (pg/ml)	2023±508.46	2007±525.57	1789.34
ESR (mm/hr)	44±13.90	42.95±4.49	36.46±3.35
CRP (mg/dl)	46.40±5.45	41.10±22.74	9.60±1.90
RF (IU/ml)	131.47±23.89	92.36±15.12	19.01±3.49
Immunological parameters			
WBCs(1×10^9)	6.94±0.28	6.69±1.76	10.05±1.50
NK Cell%	8.50 ± 0.46	8.60 ± 0.85	11.33 ± 0.47

Table 4. Possible therapeutic role of Al-hijamah in treating different autoimmune diseases

N.B. Autoimmune diseases have common criteria that are presence of autoantibodies and inflammatory mediators

Autoimmune Disease	Characterized by presence of: (4)	Possible therapeutic role of Al-hijamah (11-12, 42, 44, 50, 71)
Systemic Lupus erythematosus	Immune complexes in serum and in the basement membrane of glomeruli, skin, endothelium, synovia of joints and kidney • Anti-double stranded DNA and anti-leukocyte antibodies • Anti-phospholipid antibody (also termed, "lupus anti-coagulant) • Polyclonal B-cell activation	• Excretion of autoimmune antibodies, cytokines and immune complexes • Enhancement of natural immunity e.g. activation of natural killer cells • Pharmacological potentiation
Rheumatoid Arthritis	• High serum soluble cytokine receptors (SIL-2 R) • High serum rheumatoid factors—IgM (or IgG/IgA) to the Fc of IgG. • Association with Epstein Barr virus and human T lymphocyte virus-1	• Excretion of autoimmune antibodies, cytokines, rheumatoid factor, soluble cytokine receptors and immune complexes • Enhancement of natural immunity e.g. activation of natural killer cells • Pharmacological potentiation
Hashimoto's thyroiditis	•Anti-thyroglobulin and anti-microsomal antibodies	• Excretion of autoimmune antibodies, cytokines and immune complexes • Enhancement of natural immunity e.g. activation of natural killer cells • Pharmacological potentiation
Multiple Sclerosis	•Antibodies to the myelin basic protein secondary to cell death • Oliogoclonal (not polyclonal antibodies) in cerebral spinal fluid	• Excretion of autoimmune antibodies, cytokines and immune complexes • Enhancement of natural immunity e.g. activation of natural killer cells. • Pharmacological potentiation
Scleroderma	•Some autoantibodies e.g. anti-centromere antibodies and anti-Scl-70 antibodies	• Excretion of autoimmune antibodies, cytokines and immune complexes • Enhancement of natural immunity e.g. activation of natural killer cells. • Pharmacological potentiation
Goodpasture's Syndrome	• Anti-glomerular basement membrane antibodies • Shared antigens between the lung (alveolar) and the glomerular basement membrane • Linear deposition of IgG and complement	• Excretion of autoimmune antibodies, cytokines and immune complexes • Enhancement of natural immunity e.g. activation of natural killer cells. • Pharmacological potentiation

Addison's Disease	• Antibodies to adrenal cell microsomes	• Excretion of autoimmune antibodies, cytokines and immune complexes • Enhancement of natural immunity e.g. activation of natural killer cells. • Pharmacological potentiation
Insulin-dependent Diabetes Mellitus	•Antibodies to glutamic acid decarboxylase	• Excretion of autoimmune antibodies, cytokines and immune complexes • Enhancement of natural immunity e.g. activation of natural killer cells. • Pharmacological potentiation
Pernicious Anemia	• Antibodies bind cell surface antigens and destroy parietal cells. •Antibodies bind to gastric cells that secrete intrinsic factor. • Antibodies bind to intrinsic factor and prevent binding of vitamin B12	• Excretion of autoimmune antibodies, cytokines and immune complexes • Enhancement of natural immunity e.g. activation of natural killer cells. • Pharmacological potentiation
Grave's Disease	• Stimulatory antibodies mimic actions of ligand (thyroxin stimulating hormone) • Get uncontrolled secretion of thyroxin which leads to hyperthyroidism	• Excretion of autoimmune antibodies, cytokines and immune complexes • Enhancement of natural immunity e.g. activation of natural killer cells. • Pharmacological potentiation
Myasthenia Gravis	• Antibodies are inhibitory and block acetylcholine binding	• Excretion of autoimmune antibodies, cytokines and immune complexes • Enhancement of natural immunity e.g. activation of natural killer cells. • Pharmacological potentiation
Ankylosing Spondylitis	Prior infection with Klebsiellapneumoniae • There is no rheumatoid factor	• Excretion of autoimmune antibodies, cytokines and immune complexes • Enhancement of natural immunity e.g. activation of natural killer cells. • Pharmacological potentiation
AcanthosisNigricans	•Antibodies to the insulin receptor that block binding of insulin to the insulin receptor	• Excretion of autoimmune antibodies, cytokines and immune complexes • Enhancement of natural immunity e.g. activation of natural killer cells. • Pharmacological potentiation
Cold Agglutinin	Antibodies that agglutinate blood	• Excretion of autoimmune

Disease	cells below 37°C	antibodies, cytokines and immune complexes • Enhancement of natural immunity e.g. activation of natural killer cells. • Pharmacological potentiation

As for Al-hijamah, it may have some advantages over plasmapheresis in clearing blood from the offending CPS without the need for the sophisticated plasma exchange transfusion (therapeutic plasma exchange) **(table 5).** During the first step in Al-hijamah, collected interstitial fluids with CPS, filtered fluids (from blood capillaries containing CPS) and hemolyzed blood cells accumulate inside the skin upliftings (domes) induced during suction steps of Al-hijamah. No intact blood cells (RBCs, WBCs and platelets) exist in this fluid mixture. Blood cells have diameters in microns that are about 100-1000 times larger than the pores of the skin capillaries (6-100 nm in diameter) and are therefore too big to pass through the pores of the skin capillaries[11-12]and cannot be filtered. Puncturing skin upliftings and applying second suction step excrete collected fluids beneath the skin barrier. Superficial scarifications open the skin barrier (1st layer of epidermis) and transmit the suction pressure to the superficial fenestrated skin capillaries to make them act as filters for exerting a pressure-dependent filtration and excretion of the small sized noxious substances circulating in the fenestrated subepidermal capillaries. Superficial nature of the skin scarifications is quite important to ensure that there is no damage to the superficial skin capillaries. However, inevitable minor trauma may occur to the capillaries at some scarification points and cause the excretion to be bloody.[42, 44, 71] Superficial skin scarifications (shartatmihjam in Arabic) represent proper practice of Al-hijamah while deep skin scarifications may injure deeper blood vessels and represent a malpractice that may cause significant bleeding.

Al-hijamah is a pressure-dependent filtration procedure that is done through the fenestrated skin capillaries using suction pressure created inside suction cups. Reported sucking pressure (from -200 to -560 hecta Pascal, equivalent to -150 to – 420 mmHg) was reported to be created inside the sucking cups during WCT.[78] This suction pressure (filtration force) is transmitted (through skin scarifications = shartatmihjam induced during WCT) to around the skin capillaries to be added to the capillary hydrostatic pressure (-33 mmHg at the arterial end of capillaries and -13 mmHg at the venous ends of capillaries)[11-12, 78] that drives fluids to the outside of the fenestrated skin capillaries against the capillary osmotic pressure (+ 20 mmHg)[11-12, 78] that drives fluids to the inside of the skin capillaries.

By mathematical calculation of pressure differences, a pressure gradient and a traction force across the skin and capillaries are created leading to increased filtration at the arterial end of capillaries at net pressure of -163 to -433 mmHg and at the venous end of capillaries at net pressure of -143 to -413 mmHg[11-12, 77-78] resulting in clearance of blood from fluids containing CPS of autoimmune diseases (autoantibodies, immune complexes and inflammatory cytokines) (tables 2, 5).

Moreover, pharmacological potentiation induced by WCT to current treatment modalities in treating autoimmune diseases was proven.[42, 44-45] This can be explained on the basis that WCT excretes CPS and facilitates the therapeutic roles exerted by the conventional pharmacological therapeutics. Interestingly, Al-hijamah is a highly recommended treatment in prophetic medicine where Prophet Muhammad peace be upon him said:" Cure is in three: in sharatamihjam, gulp of honey and cauterization. I do not recommend my nation to cauterize". [79]

Al-hijamah for treating other autoimmune diseases

Compared with RA, other autoimmune diseases may have a similar pathogenesis and blood chemistry to some extent in which CPS may include autoantibodies, immune complexes, inflammatory mediators, cytokines,

products of autoreactive immune cells and others **(tables 3-5).** Al-hijamah-induced non-specific blood clearance from disease CPS, activation of natural immunity, pharmacological potentiation, analgesic effect and other therapeutic benefits [11-12, 42] may be promising in treating such diseases. Based on that, Al-hijamah may be a promising treatment for autoimmune diseases through its serum and local interstitial fluid clearance effect from CPS. Autoimmune antibodies that are present in serum of autoimmune patients were reported to be excreted outside the human body through Al-hijamah,[45] which may be beneficial in inhibiting the progression steps of pathogenesis of autoimmune diseases and in potentiating the therapeutic effects of current pharmacological treatments.

In conclusion, Al-hijamah may be promising in treating different autoimmune diseases **(Table 6)** as a sole treatment or adjuvant treatment to current treatment modalities. Al-hijamah may be superior to plasmapheresis (plasma exchange transfusion **(72-73, 81-83)** in many points when treating autoimmune diseases **(Tables 4-6).**

Table 5. Differences between Al-hijamah and plasmapheresis (therapeutic plasma exchange)

	Plasmapheresis (72-74, 81-83)	**Wet cupping therapy (Al-hijamah) (11-12, 42, 44, 71)**
Definition	Hematological procedure for separating blood cells from plasma through a specific plasmapheresis machine	Percutaneous excretory procedure for excreting CPS from plasma and interstitial fluids
Scientific principle	To discard autoantibodies from plasma	Pressure-dependent excretion of offending substances in plasma and interstitial fluids.
Criteria	Sophisticated, risky to some extent and expensive	Simple, safe and economic
Value	Excretes autoantibodies from plasma	Excretes CPS (autoantibodies, immune complexes, cytokines and inflammatory mediators) from plasma and interstitial fluids
Where can it be done?	In hematology departments in hospitals	Outpatient clinic
Repeatability	May be repeated (higher risks)	Easily repeatable (no risk or harm)
Indications	For therapeutic indications as in autoimmune diseases e.g. Goodpasture's syndrome, myasthenia gravis, Guillain-Barre syndrome and SLE.	Preventive and therapeutic for a wide range of diseases e.g. autoimmune diseases and others.
Steps	Assessing hematological indices and plasma volume, separating plasma from blood cells, returning blood cells and a plasma substitute to patient.	Demarcation of skin points, sterilization, suction of skin inside cups, scarifications, 2nd suction and sterilization
Duration	1-3 hours	About 30 minutes
Route	Venous line	Percutaneous
Before the procedure	Control bleeding tendency, assess blood volume and volume of plasma to be excreted	Control bleeding tendency
Complications	Bleeding, protein loss	Reversible skin mark

Other benefits	None	Confer many immunological and pharmacological potentiation benefits[42]
Contraindication	Bleeding tendency	No contraindication (hemophilia should be controlled first)
For treating rheumatoid arthritis	Not indicated	Proved to be beneficial in decreasing pain, excreting rheumatoid factor, excreting SIL-2R and increasingthe count of natural killer cells in patients' sera
Needs prior calculation of blood volume and plasma volume	Essential	No
Excretion of antibodies present in plasma	Sudden massive and may lead to rebound increase in production of autoantibodies. Should be done under the umbrella of cytotoxic drugs.	Gradual not causing rebound. Repeatability of Al-hijamah may benefit patients. More gradual excretion of all CPS including autoantibodies.
Necessity for replacement fluids	Necessary. Replacement fluids during plasma exchange include albumin, electrolyte solutions, hydroxy-ethyl starch, fresh frozen plasma, or purified protein products such as individual clotting factors or antithrombin III.	No need
Blood cells separation from plasma	A must. Done inside plasmapheresis machine	Not done. Filtered part of plasma containing CPS is excreted out during the process (no machine is used)
Needs simultaneous immunosuppressive therapy	Essential to avoid rebound increase in producing autoantibodies	No
Treat coexisting diseases	No	Yes e.g. hypertension and hyperlipidemia
Other names	Therapeutic plasma exchange	Prophetic method of WCT (Al-hijamah), triple S technique.

Table 6. Therapeutic benefits of Al-hijamah for patients having autoimmune diseases

1. Enhances the natural immunity (through inducing physiological leukocytosis, natural killer cell lymphocytosis[45], enhances production of immune stimulatory cytokines and suppresses production of immune inhibitory cytokines)**[84]**

2.Suppresses the abnormal pathological immunity through serum clearance from causative pathological substances:

- Suppresses the autoimmune reactions through excreting circulating autoantibodies (e.g. rheumatoid factor in rheumatoid arthritis).[45]
- Suppresses the autoimmune reactions through excreting the antigen-antibody complexes.
- Suppresses the autoimmune reactions through excreting the related inflammatory mediators (e.g. soluble interleukin-2 receptors in rheumatoid arthritis).[45]

3. Suppresses the autoimmune reactions through clearing serum from ferritin (marker for autoimmune diseases)(43).

N.B. Pathological roles of ferritin in autoimmune diseases include: *[58-62]*

.Marker of disease activity in SLE.

.Reported to increase in SLE, diabetes mellitus, multiple sclerosis, juvenile RA

and catastrophic variant of antiphospholipid syndrome.
. Involved in the pathogenesis of chronic anemia in autoimmune diseases.
.Lowering serum ferritin is associated with a good response to treatment.

4. Exerts potent analgesic effects via several mechanisms e.g. serum clearance from pain-mediating substances as substance P.[54]
5. Potentiates therapeutic effects of pharmacological treatments.[45]
5. Minimizes drug-induced side effects e.g. Al-hijamah-induced physiological leukocytosis counteracts methotrexate-induced leucopenia.[45]
6. Al-hijamah may treat associated medical conditions and reduce the required dose and frequency of drug administration.[42]
7. Al-hijamah may treat associated diseases and clears serum significantly from LDL-cholesterol, triglycerides and total cholesterol (may guard against premature atherosclerosis).[42-43]

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Conflict of interest
The authors declare that there is no conflict of interest.

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