Current Understanding and Significance of 
*Istifragh-e-Dimagh* (Brain Waste Clearance) - A Review

Anisurrahman

Professor, Department of Ilaj-Bit-Tadbeer (Regimenal Therapy)

State Unani Medical College, Prayagraj (Allahabad), Uttar pradesh, INDIA

Abstract

*Istifragh* or *tanqiya-e-badan* (body waste clearance) is an important therapeutic modality, prevalent in Unani System of Medicine, applied to treat various chronic diseases. Brain, like other parts of the body, needs to maintain homeostasis to function properly, and that requires continuous removal of toxic wastes. Brain possesses specific waste disposal system. The glymphatic system serves as a brain waste disposal system. BBB also facilitates the efflux of toxic metabolites out of the brain. The brain’s waste consists of metabolites, and proteins such as amyloid-beta, tau and alpha-synuclein proteins etc., which can form aggregates that are deleterious to brain. Sleep deprivation, aging, and many other brain pathologies (i.e. stroke, ischemia, tumour, injury etc.) may disrupt glymphatic function. Some non-pharmacological therapeutic modalities such as exercise, sleep, sleeping posture, intermittent fasting and dietary regimens (omega-3 fatty acids, resveratrol etc.) are powerful drivers of glymphatic transport. Unani herbal drug, *Ustukhuddus (Lavandula stoechas L.)* is also used for *istifragh-e-dimagh* or *tanqiya-e-dimagh* in Unani System of Medicine since long time. This review addresses current scientific knowledge regarding understanding and significance of *Istifragh-e-dimagh* with special reference to prevention and/or treatment of chronic neurodegenerative diseases.

Key Words: *Istifragh; Istifragh-e-dimagh; Glymphatic system; Alzheimer’s disease; Ustukhuddus (Lavandula stoechas L.)*

Abbreviations


1. Introduction

*Istifragh* or *tanqiya-e-badan* (body waste clearance) is fundamental principle for the treatment of chronic diseases, prevalent in Unani System of Medicine. *Istifragh* is an Arabic word, meant for elimination of metabolic wastes from the body. Metabolic wastes are the main culprits of diseases and aggravates the disease process if remain stagnant in the body. The concept of *istifragh* is described in the chapter of *Asbabe-sitta-zarooriya*. A number of pharmacological as well as non-pharmacological therapeutic modalities are adapted to induce *Istifragh* in Unani System of Medicine, when treating various chronic ailments [1,2,3,4,5,6,7]. The brain is a very expensive organ, although it takes up only 2% of the body’s mass, it uses about 20% of the body’s total energy in order to work efficiently. Brain never stops working, and its processes generate toxic wastes. As age expectancy increasing in many countries, prevalence of neurodegenerative disorders are also increasing. Currently, no cure is available although the risk of developing such diseases can be prevented. Proteinopathies are key pathological features of age related neurodegenerative diseases. Clearance of such proteins from the brain is essential to prevent the development of such diseases. Body clears its toxic wastes via lymphatics but the brain does not use that system. Brain possesses specific waste disposal system and is essential to maintain brain homeostasis and its proper functioning. The glymphatic system serves as a brain waste disposal system. In 2012, using fluorescent markers in mice Maiken Nedergaard and her colleagues at the University of Rochester Medical Centre (URMC) discovered the glymphatic system. Because of similarity to the lymphatic system, combined with the role played of glial cells (astrocytes), this brain waste clearance system eventually became known as the ‘glial-lymphatics’, g-lymphatics and finally the ‘glymphatic’ system. Glymphatic brain clearance mechanisms depends on interchange of CSF and ISF that allows waste to be transported to the CSF and transported out of the brain. AQP-4, located on astrocyte end feet, are the main structural components of glymphatic pathway. Changes in AQP-4 expression and polarization are associated with disturbances in glymphatic function. Glymphatic system is more than just the brain’s waste disposal system. Researchers found that it also plays roles in the distribution of growth factors, brain function modulators, glucose, lipids, and amino acids.
Sleep deprivation and aging disrupt glymphatic function. Accumulation of amyloid beta proteins in the walls of cerebral blood vessels further reduces glymphatic transport. Non-pharmacological healthy life style regimens such as exercise, sleep, sleeping posture, intermittent fasting, and dietary regimens (i.e. omega-3 fatty acids and resveratrol, e.t.c.) are powerful drivers of glymphatic transport [8,9,10,11]. In addition to glymphatic pathway, the blood brain barrier (BBB) also critical component in the maintenance of brain homeostasis. BBB also facilitates active nutrients transport to the brain and efflux of toxic metabolites out of the brain. Unani herbal drug, Ustukhuddus (Lavandula stoechas L.) is also used for tanqiya-e-dimagh in Unani system of Medicine [12,13], but the efficacy of this drug on the brain clearance system has not yet been evaluated. In this review article, I will discuss the underlying mechanisms and significance of istifragh-e-dimagh with special reference to prevention and / or treatment of chronic neurodegenerative diseases in the light of current scientific knowledge.

2. Source of information

Literature related to istifragh-e-dimagh / tanqiya-e-dimagh (brain waste clearance) were collected from various UnaniTibbi books. Current scientific research articles were also searched online from Pub Med and Google Scholar through different key words like istifragh, istifragh-e-dimagh, glymphatic system, Alzheimer’s Disease, ustukhuddus etc. The articles related with istifragh-e-dimagh (brain waste clearance) were included in this review.

3. Review and discussion

3.1. Mechanisms of brain waste clearance

3.1.1. Brain Waste Clearance and Paravascular Network (Glymphatic system)

Maintaining the status quo of the cellular compartment in the brain is essential for correct functioning of neurons. Thus the brain is protected by being separated from the rest of the body by a set of barriers. These barriers hinder entry of unwanted substances from the circulation, but at the same time provide for the removal of potentially toxic substances that have entered or been produced within the brain. There are numerous mechanisms for reducing entry of unwanted substances in the brain. It is also equally important to have some means of eliminating unwanted substances including those that have gained entry and those that have been formed within the brain. There are three possible pathways by which substances can be removed from the brain parenchyma: via blood brain barrier; via metabolism to different substances; or via paravascular/perivascular routes. The subarachnoid space is continuous with the brain’s paravascular spaces (PVS), thin cavities that surround and follow the penetrating arteries and veins. Paravascular network or glymphatic system is connected to a lymphatic network associated with meninges, cranial nerves, and large vessels existing in the skull. The pioneering studies documented that metabolic waste products were transported from ISF space and out of the brain via the paravascular pathway. The exchange through the glymphatic system has been suggested to be dependent on the water channel AQP-4, present in the astrocytic end feet. The glymphatic system and waste clearance process in the rodent brain was described as a 3 step serial process as follows; (1) CSF is continuously transported from basal cisterns and into sub arachnoid spaces; and from subarachnoid spaces, CSF enters the periarterial spaces in bulk flow; (2) CSF is propelled from the periarterial space into ISF space facilitated by AQP-4 on astroglial end feet, a process enabling CSF-ISF mixing and waste soluble clearance; and (3) The CSF-ISF fluid mixed with interstitial waste solutes is subsequently transported to perivascular space, from where it eventually exits into systemic circulation via cervical lymphatic vessels and are ultimately degraded in the liver.[11,14,15].

To evaluate whether amyloid – beta is cleared by glymphatic pathway, Illif et al. Injected fluorescent or radio-labelled amyloid- beta into the mouse striatum, and found that amyloid – beta was repeatedly cleared from the mouse brain along the glymphatic paravenous efflux pathway[11]. Furthermore, imaging of CSF tracer movement in AQP-4 knock-out mice revealed a 65% reduction in CSF fluid movement through the parenchyma compared to wildlife control mice and a clearance of injected radio-labelled amyloid- beta, which was reduced by 50%[11]. It was therefore proposed that the paravascular glymphatic pathway driven by AQP-4 dependant bulk flow constitutes a major clearance pathway of interstitial fluid solutes from the brain parenchyma[16].
3.1.2. CSF Production

CSF comprises 10% of the total fluid volume[17]. The CSF flows through the four ventricles that are linked by channels or foramina into the subarachnoid space of the cortex and spinal cord. From the cortical subarachnoid space it penetrates the brain parenchyma paravascularly and bathes the brain before it exits the CNS and drains into the lymphatic system. CSF is thought to be produced primarily by choroid plexuses, which are expansions of the ependymal epithelium, lining the lateral, third, fourth ventricles [18]. CSF production at the choroid plexus is mediated by exchange and transport of ions (especially Cl⁻, Na+ and HCO₃⁻) across the epithelial cells, which generates an osmotic gradient that derives the movement of water from the blood to the ventricle lumen. The Na⁺/K⁺-ATPase localized in the epical membrane of the choroid plexus epithelial cell is central to CSF production [19].

3.1.3. Motive force for Glymphatic Drainage

Glymphatic transport of CSF along the paraarterial space, followed by convective flow through the brain parenchyma, and exit of CSF-ISF along the paravenous space to the cervical lymph system, is an energy requiring process that is driven by multiple mechanisms. The constant production of CSF by the choroid plexus creates a pressure that dictates the direction of the fluid flow through the ventricular system to the subarachnoid space. In addition, several lines of work show that respiration is instrumental in movement of CSF through the aqueduct [20]. Entry of CSF along the paravenous space is crucial for facilitating glymphatic ISF-CSF exchange and clearance function. Experiment suggests that glymphatic flow is pulsatile, is driven primarily by cardiac cycle[20].

3.1.4. Motive force for Intramural Periarterial drainage (IPAD)

ISF passes from the brain parenchyma into basement membranes of capillaries and flow out of the brain along smooth muscle cell basement membrane in the walls of arteries. This pathway has been termed as IPAD [21,22]. With advancing age the stiffness of arterial walls, this pathway fails its function[21,22]. Prior to the build-up of plaques in the brain, amyloid-beta accumulates in the walls of cerebral blood vessels as cerebral amyloid angiopathy (CAA)[22]. It is important not to confuse the IPAD pathway with the Virchow- Robin Spaces, which are often referred to as paravascular spaces. The basement membrane forming the IPAD does not actually constitute a space, but rather a fluid filled protein matrix. The evidence indicate that ISF enters the BM at the capillary level and flows toward the lymph nodes in the neck via the BM of cerebral arteries. This suggests that counterintuitive phenomenon of ISF flow occurs in the reverse direction to blood flow[21]. A widely accepted hypothesis for driving mechanism of this reverse perivascular drainage is vasomotion that is contraction and relaxation of cerebro-vascular smooth muscles. Arterial pulsations can’t drive intramural periarterial drainage [21,23,24].
3.1.5. Clearance of Amyloid- beta from the Brain Parenchyma

Accumulation of amyloid-beta in the brain parenchyma and deposition of in the walls of arteries are both closely associated with the development of Alzheimer’s disease. Amyloid-beta may be removed from the brain via metabolism in brain parenchyma, via efflux across the BBB or paravascular / perivascular efflux[25]. Amyloid-beta proteins are produced mainly by neurons and some other cell types by cleavage of the membrane bound amyloid precursor protein (APP)[26]. There is evidence that plaques in the brain can be removed by reducing the ISF concentration of amyloid-beta[27]. However, it is likely that this only occurs if the amyloid-beta concentration can be reduced to levels below those present before aggregate formation began[28]. This can be achievable by inhibition of amyloid production and enhancement of amyloid – beta clearance[29]. In the young, amyloid-beta proteins are present in soluble form and eliminated as rapidly as it is produced , about 7-8% of the total soluble amyloid-beta being replaced each hour[30]. Monomeric and small oligomeric forms of soluble amyloid-beta are cleared from ISF by atleast four routes: incorporation into metabolism, plaques[31], efflux across BBB[32] and efflux via paravascular/perivascular routes[33].

3.1.6. Aging and Brain Waste Clearance

Glymphatic system seems to clear brain waste efficiently until the age of reproductive life span, then the system seems to fail gradually with advancing age[34]. In old mice, a decrease in AQP-4 expression and reduced pulsations of the arterial wall led to a 40% reduction in amyloid- beta clearance from the brain[35]. Glymphatic activity in old mice was observed to be reduced by 80-90%[34]. In aged brains, the AQP4 channels on astrocytic endfeet relocate to the astrocyte’s soma due to astrogliosis, slowing the rate of CSF-ISF exchange[36]. In addition, breathing rates during sleep increases with age due to decreasing lung efficiency. These shallower breaths will decrease intracranial pressure and weaken glymphatic clearance. The strength of penetrating arterial pulsations also decreases with age[37].

3.2. Non-Pharmacological therapeutic modalities and Istifragh-e-dimagh (brain waste clearance)

3.2.1. Sleep and Brain Waste Clearance

Generally, sleeping is considered as an unconscious state, in which the one may be aroused. During sleep the brain is less responsive to external stimuli, which is why individuals do not respond while sleeping. Sleep is needed to regenerate parts of the brain so that it can continue to function normally. Disruptions of circadian rhythm and fragmented sleep are connected to AD and PD in a bi-directional manner. Sleep disturbances are both a symptom and a potential contributor of these diseases[38]. Glymphatic function is almost exclusively active in the sleep stage. In healthy humans, studies have shown that one night of sleep deprivation leads to increases in amyloid-beta plaques in the hippocampus, ISF tau and CSF tau and α-synuclein[39]. Chronic insomnia patients had higher CSF levels of amyloid-beta[42] than normally sleeping individuals[40]. In terms of glymphatic function, sleep deprivation induces reactive astrocytes and reduces perivascular/paravascular flow and waste clearance[41]. Sleep induces brain waste clearance via several mechanisms: amyloidogenesis appears to be increased via increased amyloid precursor protein (APP) cleavage as a result of sleep deprivation[42], while clearing via glymphatic pathways is simultaneously reduced. Sleep deprivation leads to changes in AQP4 expression[41]. Chronic stress caused by sleep deprivation reduces CSF reflux and increases amyloid-beta build up in mice[43]. Reduced brain clearance appears to be mediated via the glucocorticoid receptor (GR), as GR agonists result in reduction of glymphatic function[43]. From this, it can be concluded that the fundamental purpose of sleep is to act like a garbage disposal for the brain. During natural sleep, levels of norepinephrine decline, leading to an expansion of the brain’s interstitial space, which results in decreased resistance to fluid flow. This is reflected by improved CSF infiltration along the perivascular/paravascular spaces and therefore increased interstitial solute clearance[44]. The increase in clearance happens specifically during non-rapid eye movement sleep, also known as quiescent sleep. Slow wave sleep, is categorized by slow oscillatory brain waves, that creates a flux of CSF within the interstitial spaces, leading to an increase in glymphatic clearance[45].

3.2.2. Sleeping Posture and Brain Waste Clearance

Gravity affects the movement of blood and CSF through the brain, and therefore sleeping position is likely play a role in the clearance of waste from the brain. Both intracranial pressure and cerebral hemodynamics are influenced by body posture. An important factor in this clearance pathway is the stretch of nerves and veins in each position. Glymphatic transport is most efficient in the right lateral sleeping position, with more CSF clearanceoccurring compared to supine and prone[46]. In the paper, “The effect of body posture on brain glymphatic transport”, researcher used a dynamic contrast MRI method along with kinetic modelling to quantify the CSF-ISF exchange rates in anaesthesized rodent’s brains in three positions: lateral, prone, and supine. The analysis showed that glymphatic transport was most efficient in the lateral position when compared to the supine or prone positions. It is interested that the lateral sleeping position is already the most popular in human and most animals[46].
3.2.3. Exercise and Brain Waste Clearance

Glymphatic flow is accelerated by exercise training. Voluntary running over six weeks restored protein homeostasis in the brain by decreasing the activation of astrocytes through an increase in glymphatic clearance [45]. AQP-4 expression in the cortex was also found higher along the paravascular space in the exercise group [45]. Polarized expression of AQP-4 are crucial for CSF inflow and the clearance of amyloid-beta. Loss of polarized expression of AQP4 in the brain contributes to the impairment of glymphatic function. [47]. Regular aerobic exercise reduces the amyloid-beta protein deposition and neuroinflammation by improving AQP-4 expression, hence increases glymphatic flow. In a study, Researcher examined aging mice to assess the effects of exercise on the disturbances of protein homeostasis in the brain. Voluntary running effectively restored the loss of protein homeostasis. Voluntary running also significantly attenuated the inflammatory activation of microglia and astrocytes. These beneficial effects were accompanied by significant improvement in glymphatic clearance [48].

3.2.4. Intermittent Fasting and Brain Waste Clearance

Fasting may be defined as partial or total abstinence from food and drink for specified, recurring periods of time [49]. Fasting most often contrasted with ad libitum feeding, which is characterized by three or more meals per day. Fasting should not be confused with starvation, a state of chronic nutritional insufficiency, which neither voluntary nor controlled, and which may culminate in organ failure and death. Most world religions, including Christianity and Islam, also incorporated fasting into their religious practices [50]. In 1900s, German physician Otto Büchinger, the first person to rigorously document the beneficial effects of fasting in many human diseases. [51]. Volter Longo, an Italian-born biogerontologist and fasting researcher in the 2000s, has recently suggested that fasting selectively activates multiple “longevity programs”, which may lead to an extended life span as well as extended health span [52]. Fasting periods longer than a day are often grouped under the broadly used term “intermittent fasting”. The most common intermittent fasting regimens are alternate day fasting (ADF) [53].

The three most commonly studied fasting are calorie restriction (CR), alternate day fasting (ADF) and dietary restriction (DR). CR is the reduction of calorie intake by a certain percentage (typically 20-40%) of ad libitum consumption. ADF consists of alternating 24 hour periods: during the feast period, fasters may consume food ad libitum; during the fast period, food consumption is restricted. DR is a reduction of one or more components of dietary intake with minimal to no reduction in total calorie intake. Islamic Ramadan fasting is similar to ADF, because both fasts incorporate feast periods and fast periods. The feast periods and fast periods of Ramadan fasting are each 12 hours in length on average [53, 54], which amounts to half of the 24-hour length for both the feast periods and fast periods of ADF. Another important difference between the two forms of fasting is that fluid intake is forbidden during the fast period of Ramadan, whereas it is permitted at all times under an ADF protocol [53, 54].

In a study, researchers confirmed the beneficial effects of IF in AD, and mechanism may be associated with increased AQP-4 polarity along the paravenous space, resulting from the reduction of AQP4-M1/M23 ratio, hence IF boosts the glymphatic clearance of amyloid-beta. Furthermore, βOHb may at least partly mediate the effect of IF on the reduction of AQP 4-M1/M23 ratio [55]. IF results in ketone body metabolism and increase in βOHb level in blood. [55]. In the brain, AQP-4 mainly exists in two isoforms: a long isoform, AQP4-M1 and a short isoform, AQP4-M23. IF downregulates the expression of AQP4-M1, decreasing the AQP 4-M1 / M23 ratio[55].

3.2.5. Omega-3 fatty acids and brain waste clearance

Long chain omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic (DHA), are predominantly sourced from marine fish [56]. EPA and DHA can also be synthesized from alpha-Linolenic acid (ALA), which is present in a number of green leafy plants, seeds, nuts, herbs, and oils, such as flax seeds, walnuts, soybean oil, canola oil, and hemp seed oil [57]. A low conversion efficiency of ALA into EPA and DHA, which varies between individuals, has been reported in a number of studies [58]. The central nervous system is highly enriched in omega-3 fatty acids. Accumulating evidence proves that increased intake of omega-3 fatty acids may confer benefits in a variety of neurological diseases. Epidemiological studies suggest that sufficient supply of omega-3 fatty acids is associated with reduced incidence of developing AD [59]. Both endogenous and exogenous omega-3 fatty acids promote amyloid-beta clearance and reduce aggregate formation by inhibiting the activation of astrocytes and protecting the loss of AQP-4 polarization. Supplementation of omega-3 fatty acids demonstrates higher CSF influx and clearance, with AQP-4 remaining polarized at the endfeet, increasing the speed of glymphatic clearance [59].

3.3. Unani herbal drug, Ustukhuddus (Lavandula stoechas L) and brain waste clearance

Ustukhuddus is one of the most important herbal drug. It is named as ‘jaroob-e-dimagh’ (broom of brain) in Unani System of Medicine. The drug is used since ancient times and was mentioned by Discorides (1st century AD) in his book “De Materia Medica”. The flowers and leaves of ustukhuddus are used commonly for the treatment of brain diseases such as nisyam (dementia), epilepsy, and brain stroke etc., Ibn e sina in his famous treatise, “Advia Qalbiya” described its efficacy in
removing the vitiated humour from the brain, but the efficacy of this drug on the brain clearance system has not yet been evaluated [60,61,62].

4. Conclusions

Currently, 47 million people worldwide suffer from dementia because of accumulation and aggregation of amyloid–beta proteins in the brain and there is no effective curative or preventive intervention. Aging highly increases the risk for cerebral amyloid angiopathy (CAA) and formation of amyloid plaques in the neurons, and considering increasing longevity in the world, the occurrence of dementia by 2050, is evaluated to be 131 million people. This increases the urgency to explore potential unconventional clearance mechanisms for toxic proteins that may contribute toward maintaining the homeostasis of brain. This review suggests that glymphatic system plays a critical role in maintaining the homeostasis within the brain by performing istifragh-e- dimagh, and non-pharmacological therapeutic modalities such as exercise, adequate sleep, lateral side sleeping posture, intermittent fasting, and omega-3 fatty acids promote brain waste clearance through mediating the function of glymphatic system. Further studies in human brain are required for assessing the association between non-pharmacological therapeutic modalities and istifragh-e-dimagh.

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None

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