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

AD: Alzheimer's disease; ADF: alternate day fasting; APP: Amyloid precursor protein; AQP-4: aquaporin -4; Aβ: amyloid-beta peptide; BM: basement membrane; BBB: blood-brain barrier; βOHB :β-hydroxybutyrate; CAA: cerebrovascular amyloid angiopathy; CNS: central nervous system; CR: calorie restriction; DR: dietary restriction; IF: intermittent fasting; ISF: interestitial fluid; IPAD: intramural periarterial angiopathy; GR: glucocorticoid receptor.

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 sub-arachnoid space is continuous with the brain's paravascular spaces (PVS), thin cavities that surround and follow the penetrating arteries and veins. Paravascularnetwork or glymphatic systemis 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 in to 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 perivenous 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 $_{1\text{-}40}$ 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].

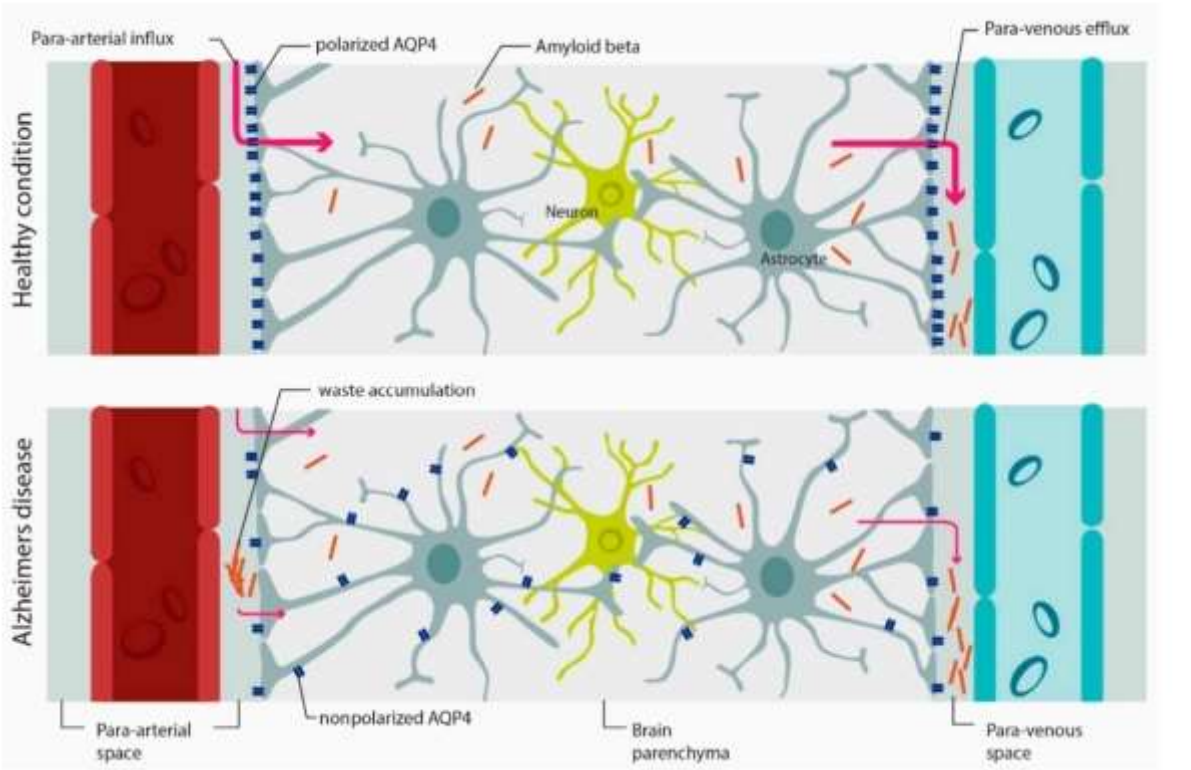

Fig.1 AQP-4 in astrocytic end feet, mediates brain waste clearance via glymphatic system.. Image modified from[34]

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 HCO_3^-) 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 sub arachnoid 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 paravascular 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 metablism in brain parenchyma, via efflux across the BBB or paravascular / perivascular efflux[25]. Amyloid-beta proteins are produced mainlyby 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 interestitial space, which results in decreased resistance to fluid flow. This is reflected by improved CSF infiltration along the perivascular/ paravascular spaces and therefore increased interestitial 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 interestitial 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 clearanceoccuring 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 APQP-4 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 is 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 organsfailure and death. Most world religions, including Christianity and islam, also incorporated regular fasting into their religious practices [50].In 1900s, German physician Otto Buchinger, 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 libitium* 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 hamp 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. Epidimiological 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 *nisyan* (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 occurance 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* .

Source(s) of funding

None declared

Conflict of interest

None

References

1. Hamdani K, Usool-e-tib, New Delhi, National Council for promotion of Urdu Language; 1998.
2. Sina A, AlQanoonFilTib (Urdu Translation by Kantoori GH), Vol1st,IdaraeKitabushifa, New Delhi.
3. IbneRushd M, Kitabul Kulliyat(Translated by CCRUM), Central Council For Research In Unani Medicine, New Delhi, 1987.
4. Razi Z, KitabulMurshid(Urdu Translation by Nadwi MR), Taraqqi Urdu Bureu; New Delhi; 2000.
5. Nafees B, TarjumawaSharh-e-Kulliyat e Nafeesi(Urdu Translation by Kabeeruddin), IdaraeKitabushifa, New Delhi.
6. Sina A, KulliyateQanoon (Urdu Translation by Kabeeruddin), IdaraeKitabushifa, New Delhi, 2015
7. Majoosi, Kamilussina(Urdu Translation by Kantoori GH), Vol 1st, New Delhi, IdaraeKitabushifa; 2010.
8. Underwood E. Neuroscience. Sleep: the brain's housekeeper? Science. 2013;342:301.10.1126/Science.342.6156.301 [Pub Med:24136944]
9. Xu Z, Xiao N, Cheny, et al. deletion of aquaporin -4 in APP/PS1 mice exacerbates brain Amyloid-beta accumulation and memory deficits. Mol. Neurodegener 2015;10:58
10. Cao X, XuH, Feng W, et al. Deletion of aquaporin-4 aggravates brain pathology after blocking of the meningeal lymphatic drainage. Brain Res Bull 2018; 143:83-96.
11. Illif JJ, Wang M, Liao Y, et al. A paravascular Pathway facilitates CSF flow through brain parenchyma and clearances of interstitial solutes, including amyloid-beta. SciTransl Med 2012;4:15
12. Siddiqi MA, Khalid M, Akhtar J, Siddiqi HH, Ahmad B, et al; LavendulaStoechas: A miracle plant, JIPBS, 2016; 3(1): 96-102.
13. Koulivand PH, Ghadiri MK, Gorji A; Lavender and nervous system, Evid based complement Alternate Med, 2013; 681304. Doi:1155/2013/681304
14. Nedergaard M; Neuroscience, Garbage truck of the brain, Science 2013; 340: 1529-1530.
15. Louveau A, Smirnov I, Keyes J, Eccles JD, Rouhani SJ, Peske JD, Derecki NC, Castle D, Mandell JW, Lee KS, Harris TH, Kipnis J: Structural and Functional features of central nervous system Lymphatic Vesseles: Natu2013re 2015; 523: 337-341.
16. Illif JJ, Nedergaard M. Is there a cerebral lymphatic system ? Stroke. 2013;44: S 93-5. 10.1161/ STROKEAHA. 112.678698[pubmed.3003748]
17. Trane AS, RngrooThrane V, Nedergaard M, Drowning stars; Reassessing the role of astrocytes in brain edema. Trends Neuroscience. 2014; 37:620-628.10.1016/ J.tins. 2014.08.010[pubmed:25236348].
18. Keep RF, Jons HC.A morphometeric study on the development of the lateral ventricles choroid plexus, plexus capillaries and ependyme in the rat. Brain Res Dev. 1990; 56:47-53.10[pubmed:2279331]
19. Johanson,CE.Neuroscience Med. 2008. Choroid plexus- cerebrospinal fluid circulatory dynamics:Impact on brain growth, metabolism and repair.
20. IllifJJ,Wang M, et al. Cerebral Arterial pulsation drives paravascular CSF- Interestitial fluid exchange in murine brain. J Neuroscince. 2013;33:18190-9.10.1523/JNUROSCI.1592-13.[PUBMED:24227727]

21. Carare R.O., Bernardes- Silva M., Newman T.A., Page A.M., Nicoll J.A., Perry V.H., et al., (2008). Solutes, but not cells, drain from brain parenchyma along basement membrane of capillaries and arteries: Significance for cerebral amyloid angiopathy and Neuroimmunology. Neuropathol. Appl. Neurobiol. 34, 131-144. 10.1111/ J. 1365-2990. 2007.00926.x [pub med]
22. Weller R.O., Galea I., Carare R.O., Minager A (2010). Pathophysiology of the lymphatic drainage system of the central nervous system: Implication for pathogenesis and therapy of multiple sclerosis. Pathophysiology 17, 295-306. 10. 1016/ J. Pathophysiol. 2009. 10. 007. [pub med]
23. Weller R.O., Hawkes C.A., Kaleria R.N., Werring D.J., Carare R.O. (2015). Whitematter changes in Dementia: role of impaired drainage of interestitia fluid. Brain Pathol. 25, 63-78. 10. 1111/bpa. 12218 [pub med]
24. Illif J.J., Wang M., Lio Y., Plogg B.A., Peng W., Gundersen G.A., et al., (2012). A Paravascular Pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid –beta. Sci Transl. Med. 4; 147 ra 111. 10. 1126/ Scitranslmed. 3003748 [pub med].
25. Tarsoff-Conway JM, CarareR.O.,Osorio RS., Glodzik I, ButlerT., Fieremans E, Axel L, Rusinek H, Nicholson C, Zlokovic BV, et al. Clearance systems in the brain- implications for Alzheimer's disease. Nat Rev Neurol. 2015;11:457-70.
26. Haass C, Kaether C, Thinakaran G, Sisodia SS. Trafficking and proteolytic processing of APP. Cold Spring Harb Prospect Med. 2012;2:a006270.
27. Cirrito JR, May PC, O'Dell MA, Taylor JW, Parsadanian M, Cramer JW, Audea JE, Nissen JS, Bales KR, Paul SM, et al. In assessment of brain interestitial fluid with microdialysis reveals plaque-associated changes in amyloid-beta metabolism and half life. Journal Neuroscience. 2003;23:8844-53.
28. Harper JD, Lansbury PT Jr. Models of amyloid seeding in Alzheimer's disease and scrapie: mechanistic truths and physiological consequences of the time-dependent solubility of amyloid proteins. Annu Rev Biochem. 1997; 66:385-407.
29. Morrone CD, Liu MZ, Black SE, McLaurin J. Interaction between therapeutic interventions for Alzheimer's disease and physiological Amyloid-beta clearance mechanisms. Front aging Neuroscience. 2015;7:64.
30. Mawuenyega KG, Sigurdson W, Ovod V, Munsell L, Kasten T, Morris JC, Yarasheski KE, Bateman RJ. Decreased clearance of CNS beta- amyloid in Alzheimer's disease. Science.2010;330:1774.
31. Ries M, SastreM. Mechanism of amyloid clearance and degradation by glial cells. Front aging Neuroscience.2016;8:160.
32. Zhao Z, Sagare AP, Ma Q,Halliday MR, Kong P, Kisler K, Winkler EA, Ramanathan A, Kanekiyo T, Bu G, et al. Central Role for PICALM in amyloid –beta blood brain barrier transcytosis and clearance. Nat Neuroscience.2015;18:978-87.
33. Peng W, Achariyar TM, Li B, Liao Y, Mestre H, Hitomi E, Regan S,Kasper T, Peng S, Ding F, et al. Suppression of glymphatic fluid transport in a mouse model of Alzheimer's disease. Neurobiol Dis. 2016; 93: 2015-24
34. Jessen NA, Munk ASF, Lundgard I, Nedergaard M. The glymphatic system: A beginnersguid. Neurochem. Res. 2015,40,2583-2599.
35. Rasmussen MK, Mestre H, Nedergaard M. The glymphatic pathway in neurological disorders. Lancet Neurology. 2018,17, 1016-1024.
36. He XF, Zhang Q, Liyang FY, Dai GY. Voluntary exercise promotes glymphatic clearance of amyloid- beta and reduces the activation of astrocytes and microglia in aged mice. Front. Mol. Neuroscience. 2017,10, 144.
37. Levendowski DJ, Gamaldo C, Luois EKS, et al., Head position during sleep: Potential implications for patients with neurodegenerative Disease. J. Alzheimer's disease Dis. 2019, 67, 631-638.
38. Abbott SM, Malkani RG, Zee PC, Circadian Disruption and human health.:A bidirectional relationship. Eur J Neuroscience 2020; 51: 567-570.
39. HolthJk, Fritschi SK, Wang C, et al. The sleep wake cycles regulates brain interestitial fluid tau in mice and CSF tau in humans. Science 2019; 363: 880-884.
40. Chen DW, Wang J, Zhang LL, et al. Cerebro spinal fluid amyloid-beta are increased in patients with insomnia. J Alzheimer's Dis 2018; 61: 645-651.
41. Liu D, He X, Wu D, et al Continuous theta burst stimulation facilitates the clearance efficiency of the glymphatic pathways in mouse model of sleep deprivation. Neuroscience Lett 2017; 653: 189-194.
42. Chen L, Huang J, Yang L, et al. Sleep deprivation accelerates the progression of Alzheimer's disease by influncing Amyloid-beta related metabolism. Neuroscience Lett 2017; 650: 146-152.
43. Xia M, Yang L, Sun G, et al. Mechanism of depression as a risk factor in the development Alzheimer's disease: The function of AQP4 and the glymphatic system. Pschopharmacology (*Berl*) 2017; 234: 365-379.
44. Plog, BA; Nedergaard M, The Glymphatic System in central nervous system Health and Disease: past, present and future, Annu Rev Pathol. Mech Dis. 2018, 13, 379-394.
45. Lee H,XieL,YuM,Kang H, FrengT,DeaneR,Benveniste H. The effect of body posture on brain glymphatic transport. J. Neuroscince, 2015,35,11034-11044 [pub med].
46. Lundgaard I, Wang W, Eberhardt A, Vinitsky HS, Reeves BC, Peng S, Nedergaard M. Beneficial effects of low alcohol exposure, but adverse effects of high alcohol intake on glympatic function. Sc. Rep. 2018,8,2246.

47. Xiao-fei He, Dong-xu Liu, Qua Zhang, Feng-ying Liang, Guang-yan Dai, Jin- sheng Zeng, Zhong Pei, Guang- qingXu, and YueLan. Voluntary Exercise Promotes Glymphatic clearance of amyloid Beta and reduces the activation of astrocytes and microglia in aged mice. Front in Mol. Neuroscience. 2017:10.144[doi:10.3389/fnmol.2017.00144].
48. Longo,VD; Mattson MP;. Fasting: Molecular mechanisms and clinical applications. Cell Meta. 2014,19,181-192[Pub Med]
49. Kerndt,PR; Naugdt, jl; Driscoll, CE; Loxterkamp,DA. Fasting: The History, Pathophysiology and complications. West Med.1982,137,379-399.
50. Buchinger, O; Das Heilfasten; Georg TheimeVerlag: Stuttgart, Germany, 1935.
51. Longo, VD; Prolonged Longevity, Youth span and juventology. Aging cell. 2019,e 12843.
52. Di Francesco, A; Di Germanio,C; Bernier M; decabo, R. A time to fast. Science . 2018,362, 770-775.
53. Aksungar FB; Eren A, Ure S; Teskino O, Ates G: Effects of intermittent fasting on serum lipid levels,Coagulation status and plasma homocysteine levels. Ann NutrMetab, 49:77-82.
54. John F Trepanowski; Richard J Bloomer. The impact of religious fasting on human health. Nutrition Journal: 2010, 9: 57
55. Jingzhu Zhang, Zhipeng Zhan, Xinhui Li, Aiping Xing, et al., Interittent fasting protects against Alzheimer's disease possible through restoring Aquaporin-4 polarity. Frontier's in Mol. Neuro.2017/10/395[doi:10.3389/fnmol.2017. 00395]
56. p.m. Kris- Etherton, J.A. Grrieger, and t.d. Etherton, Dietatry reference intakr for DHA and EPA, prostagandins leukotrients and essential fatty acids, vol. 81/2-3, 99-104, 2009.
57. B.C Davis and pm kris etherton, Achieving optimal essential fatty acids status in vegeterian: current knowledge and practical implications. Americal Jounal of clinical nutrition. Vol. 78. /3/.640-646, 2003
58. J.T. Brena, N. Salem, et al. Alpha linolenic acid supplementation and converson to omega-3 long chain polysaturated fatty acids in humans. Protaglandins, leukotrients and essential fatty acids, vol.80/2-3/85-91,2009.
59. Ren H; Luo C; Feng Y; Yao X; Shi Z; Liang F; Su H. Omega -3 fatty acids promote amyloid beta clearance from the brain through mediating the function of the gymphatic system. FASEB J. (2016), 31 / 1/ 282-293.
60. Ibne sina. AlQanoon Fil Tib (Urdu Translation by Kantoori GH), New Delhi: Idara Kitabusshifa; Vol. 2 (2007):277.
61. Ghani N. Khazian al Adwiya. New Delhi. Idara Kitabushifa (2011)
62. Khan Azazm. Muheet e Azam. New Delhi. CCRUM/1/ (2012):307.