# Unani Medical Non Pharmacological Regimens Display Hormesis-A Review

**Anisurrahman**

**Professor; Department of Ilaaj-bit-Tadbeer (Regimenal Therapy)**

**State Unani Medical College, Prayagraj (Allahabad), U.P., INDIA (211016)**

**Abstract:** A number of Unani Medical non-pharmacological regimens namely *Ghiza-i-Tadaabeer* (dietary regimens), *Hammam* (turkish bath) and *Riyazat* (exercise), etc., have been used since ancient times in the treatment of numerous human pathologies. Their purpose is to maintain cellular homeostasis by regulating various metabolic pathways. These regimens are very useful in promoting immune homeostasis and longevity, and alleviating aging, age-related disorders, and autoimmune disorders. Biological mechanisms, by which these regimens effective in several diseases, are still not completely understood, but it is known that neuro-endocrine and immunological responses are involved, leading to anti-inflammatory, analgesic and antioxidant effects in different pathological conditions. Hormetic behaviour of these regimens can be related to non specific factor such as stress, which induces the production of heat shock proteins, resulting in the enhancement of *istifaragh* (detoxification) by a process referred to as chaperone mediated autophagy (CMA). Hormesis is a process in which exposure to a low dose of a physical, chemical, thermal or physiological agent that damaging in higher doses induces an adaptive beneficial effect on the cell or organism. A little bid of bad can be a good thing. This is the science of hormesis. Hormesis have bio protective functions including antioxidant activity, DNA repair, apoptosis, detoxification and immune homeostasis. In this article, I have described the hormesis hypothesis of the effectiveness of *Ghiza-i-Tadaabeer* (dietary regimens), *Hammam* (turkish bath) and *Riyazat* (exercise) in various pathological conditions.

**Key Words:** hormesis; heat shock proteins; autophagy; *istifaragh*; *ghiza-i-tadaabeer*; *hammam*; *riyazat*.

## 1. INTRODUCTION

A number of non-pharmacological therapeutic regimens including *ghiza-i-tadaabeer* (dietary interventions), *hammam* (turkish bath) and *riyazat* (exercise) etc. have been used in unani medical system to treat various human pathologies[1].These regimens promote the functioning of *tabiyat*[1] (medicatrix naturae) to maintain cellular homeostasis. Hippocrates[1] (460-377 BC) stated that "*tabiyat*[1] (medicatrix naturae) is prime healer of the body". It maintains cellular homeostasis by regulating different metabolic pathways. Biological mechanisms are not fully understood by which Unani medical regimens effective in various human pathologies. It is hypothesized that hormesis partly plays a role in the effectiveness of these regimens. Hormetic effects can be related to stress. Physiological systems respond acutely to stress to minimize homeostatic disturbances, and typically adapt to chronic stress to enhance tolerance to that or a related stressors. Low levels of stress from physical, chemical, thermal and biological stressors often, but not always, result in the functional improvement of cells, tissues, organs and organisms and considered the basis of hormesis. For example: moderate level of exercise promotes good health, whereas excessive levels are debilitating[2]. In pharmacology, many chemicals are known to have opposite effects as a function of dosage (e.g., the antibiotics, penicillin, erythromycin and streptomycin promote bacterial growth at low doses and kill at higher doses). It has long been recognized that mild and intermittent forms of stress can promote mental and physical functions whereas extreme stress is more likely to cause mental anguish and physical ailments. It means that only the dose or amplitude makes a thing or condition harmful or beneficial. Several studies showed that many therapeutic interventions exhibit biphasic dose response on cells with mild to moderate levels of stress, activating signaling pathways that result in increased expression of genes encoding cytoprotective proteins including antioxidant enzymes, protein chaperones, growth factors and mitochondrial proteins[3]. In this review article, I have discussed the hormesis processes involved in the *Ghiza-i-tadaabeer* (dietary regimens), *hammam* (turkish bath) and *riyazat* (exercise) that mediate different health benefits.

## 1. REVIEW

**2.1. Hormesis.** Hormesis is a biphasic dose response phenomenon, characterized by stimulation by low doses and inhibition by high doses of any physical, chemical agents. Hormesis is an enhancement of "natural defense mechanism". The main hormetic agents identified so far are food restriction, exercise, heat, dehydration, irradiation, pro-oxidants, hyper-gravity and antibiotics[4]. According to hormetic agents it can be nutritional hormesis, thermal hormesis, exercise hormesis, radiation hormesis, redox hormesis and chemical hormesis, etc. Hormesis was first reported in 1943 issue of phytopathology by C. Southam and J. Ehrlich, who described an oat bark compound that promoted fungal growth at low doses but strongly inhibited growth at higher doses. The term derives from the Greek word "hormo", meaning to excite or stimulate[5].

Researchers at the University of Massachusets have proposed that hormetic stresses induce cellular adaptations brought on by activation of an "anti-stress" gene. In article "hormesis and adaptive cellular control systems" in journal dose-response, *Melvin anderson and Zhang et al(2008)* present evidence that hormetic stressors are first detected by molecular sensors, which activate transcription factors and regulate the expression of anti-stress gene. These genes in turn activate a cascade of homeostatic pathways that is adaptive responses which protect the cells from stressful environments. One example is the activation of " heat shock proteins" expressed by cells as an adaptive response to heat stress allowing the cell to resist heat denaturation of cellular proteins[6].Hormesis is not only associated with environmental conditions, it also related to the normal physiological conditions of the cells and organisms. For example: exposure of neurons to the excitatory neurotransmitter glutamate during normal activity, results in oxidative stress accompanied by activation of hormetic pathways that help the neurons cope with more severe stress. However excessive stimulation of glutamate receptors can destroy neurons in a process called excitotoxicity [7] [8].

Hormesis is a fundamental concept in evolutionary theory. From the beginning through the present time, life on earth has existed in harsh environments in which cells are often exposed to free radicals and toxic substances. To avoid extinction, organisms have developed complex mechanisms to cope with the environmental hazards. Typically, such hormetic response pathways involve proteins such as ion channels, kinases and deacetylases, and transcription factors which regulate the expression of genes that encode cytoprotective proteins. Several major categories of hormetic stress resistance proteins have been identified including heat shock proteins, anti-oxidant enzymes such as superoxide dismutases and glutathione peroxidase, and growth factors such as insulin- like growth factors and brain derived neurotrophic factor[8] [9] . In some cases organisms have used the chemical properties of toxic agents, incorporating them into cellular signaling or metabolic pathway[8].

One of the most widely studied types of experimental hormesis, called preconditioning ischemia, occurs when an organ are subjected to a brief mild ischemia[8] [10]. The cells become resistant to being killed by a full- blown heart attack or strock. Ischemia exhibits a biphasic dose response, with brief period of ischemia being protective and prolonged periods resulting in cell damage. The cellular and molecular mechanism underlying preconditioning ischemia hormesis are being elucidated and may involve oxidative stress-induced cytoprotective signaling pathways involving activation of kinases, changes in mitochondria, and the expression of genes encoding antioxidant enzymes and protein chaperones[8] [11].

A common observation in sudies of hormesis is that exposure to low levels of one type of hormetic agent can promote cells/ organisms against more than one type of stress. For example, exposure of cells to mild heat stress can protect them from being damaged by oxidative stress or toxins[8] [12]. Similarly, when cells are exposed to a low doses of the mitochondrial uncoupling agent 2,4-dinitrophenol they are less vulnerable to being killed by ischemia[8] [13]. The cross model of hormesis in biological systems, may explain the broad benefits of exercise, heat shock and dietary interventions [8] [14]. Recent findings suggests that health benefits of many phytochemicals may also be conferred by cross-model hormesis mechanisms, in which a phytochemical activates one or more adaptive cellular stress response pathways[8] [15].

**2.2. *Ghiza-i-tadabeer* (dietary regimens) and hormesis.** There are three methods practised in unani medicine viz., *ilaaj-bil-tadbeer wal ghiza* (regimenal herapy including dietotherapy), *ilaaj-bil-dawa* (pharmacotherapy) and *ilaaj-bil-yad* (surgery)[16]. Unani medicine deals with the different types of diets like *ghiza-e-dawai*, *dawa-e-ghizai*, *ghiza- e - qaleelul taghziya*, *ghiza-e- jayadul kaimoos*, *ghiza-e- raddiul kaimoos*, *kaseef ghiza*, *lateef ghiza*, *motadil ghiza* etc. A number of books on dietics are written by the scholars of unani medical system. Some of them are: *Manafeul Atima wal Ashriba* by Rabban Tabari, *Kitab fil Aghzia* by Rabban Tabari, *Fit Tadabeer-al- Asehha bil makul wal mashroob* by Hunain bin Ishaq and *Kitab Aghzia-tul- Marza* by Najeebuddin Samarqandi. The great chemist, physician, Astronomer and philospher Rhazes (865-925) is regarded as great nutritionist and dietician of that period and a pioneer of dietetics[17] [18] [19].

The impact of dietary factors on health and longevity is increasingly appreciated. The most prominent dietary factor that affects the risk of many different chronic diseases is energy intake that is intake of food quantity. Excessive calorie intake increases the risk of various diseases. Low calorie intake increases life span and protects the body from various diseases, in part, by hormesis that enhance cellular defense mechanism. Some specific dietary components may also exert health benefits by inducing hormesis[20].

***2.2.1. Taqleel-e-Ghiza* (Dietary Energy Restriction-DER) and hormesis.** Studies on animals show that DER either in the form of reduced food intake or intermittent fasting can increase the resistance of cells to various types of stress. Nerve cells in the brain of animals, maitained on DER exhibited increased resistance to neurotoxins in experimental models relevant to epilepsy, Huntigton's disease, Parkinson's disease and Alzheimer's disease[21]. Studies on humans also suggest that DER can counteract disease processes. For example, alternate day fasting improved symptoms and reduced markers of inflammation and oxidative stress in asthma subjects[20] [22]. DER was effective in protecting heart and brain cells against ischemic injury in models of myocardial infarction and stroke[23]. DER promotes longevity. In an animal studies, mortality from natural causes is significantly reduced that have been maintained on DER compared to control group that consumed a normal diet [24].

Studies have revealed several biochemical and molecular changes, involving hormesis mechanisms, in animals maintained on DER regimens. Levels of HSPs, which serve a chaperone function, have been shown to be increased in several tissues of animals maintained on DER. For example, levels of HSPs are increased in liver cells of rats maintained on DER[25]. Other type of chemical molecules upregulated by DER is antioxidants [20] [26]. Upregulation of antioxidants is related to hormesis[20]. Growth factors play important role in regulating hormesis. For example, mild ischemia induces the expression of vascular endothelial cell growth factor (VEGF) in both heart and brain and electroconvulsive shock increases the brain derived neurotrophic factors (BDNF). These growth factors activate signaling pathways that protect cells against oxidative and metabolic damage. Interestingly, DER may not induce a hormetic response in all cell types. For example, motor neurons in the spinal cord fail to upregulate the HSPs [20].

**2.2.2. *Ghiza-i-Ajza* (dietary components) and hormesis.** Evidence from epidemiological studies suggests beneficial roles of dietary phytochemicals in protecting against chronic disorders such as cancer, and inflammatory and cardiovascular diseases. Emerging findings suggest that several dietary phytochemicals also benefit the nervous system and, when consumed regularly, may reduce the risk of disorders such as Alzheimer's and Parkinson's disease. The evidence supporting health benefits of vegetables and fruits provide a rationale for identification of specific phytochemicals responsible, and for investigation of their molecular and cellular mechanisms of action. One general mechanism of action of phytochemicals that is emerging from recent studies is that they activate adaptive cellular stress response pathways. From an evolutionary perspective, the noxious properties of such phytochemicals play an important role in preventing insects and other pests from eating the plants. However at the subtoxic doses ingested by humans that consume the plants, the phytochemicals induce mild cellular stress responses. This phenomenon has been described as hormesis[27].

Over the past three to four decades, convincing evidence has emerged that vitamin D generates positive and important biological responses in the immune, cardiovascular, muscular and nervous system as well as involvement in cell cycle control and thus of cancer disease process[28]. Reasons behind this that vitamin D provides protection against low level radiation damage. In addition, the positive and important role of vitamin D is in the aging process. There is substantive evidence that vitamin D acts as a hormetic agent. Laboratory studies suggest vitamin D-induced biphasic dose-responses[29]. Human studies suggest that vitamin D in low doses have stimulatory effects promoting epidermal wound healing, in contrast to high doses inhibiting psoriasis[30]. Epidemiological and other studies support the protective role of fruits and vegetables against cancer, including prospective epidemiological studies of atomic bomb radiation survivors[31].The consumption of green tea has recently attracted much attention because of its beneficial effects. Polyphenolic compounds found in green tea include epigallocatechin-3-gallate (EGCG), epicatechin-3 gallate (ECG), epigallocatechin (EGC) and epicatechin (EC), and their intake has been associated with reduced risk of coronary artery disease[32]. A recent study reports that EGCG upregulates heme-oxygenase-1(HO-1) by activation of the nuclear factor erythroid 2- related factor-2 (Nrf2) pathway in endothelial cells, conferring resistance against $H_2O_2$ - induced cell death, suggesting a hormetic mechanism of action[33].

Curcumin, found in turmeric, partly, acts as hormetic agent. It has extensive therapeutic effects via its antioxidant, anti-inflammatory, and antiproliferative properties. Preclinical *in vitro* and *in vivo* data have shown curcumin to be an effective treatment for multiple cancers. These effects are derived by curcumin's ability to induce autophagy. This phenomenon is referred to as hormesis. Curcumin is as efficient in the removal of radicals as well known antioxidants-Vitamin A, Vitamin C and vitamin E, and mimics the function of superoxide dismutase[34]. Several beneficial effects of curcumin for the nervous system have been reported. In animal model of stroke curcumin treatment protected neurons against ischemic cell death. A hormetic mechanism of action of curcumin is suggested from studies showing that levels of expression of HO-1 were increased in cultured hippocampal neurons treated with curcumin[35]. Resveratrol is present in significant amounts in certain fruits and vegetables including grapes, red wine, blueberries and craneberries, as well as in peanuts and walnuts. Resveratrol is a phytoalexin displays hormesis. A laboratory studies suggest that resveratrol significantly reduces the myocardial infarct size[36].

2.3. ***Hammam* (turkish bath).** *Hammam* is an example of whole body heat stress. It is a therapeutic regimen , employed in unani medical system to relieve mental stress, enhance immunity and promoting longevity, and alleviates the risk of age relate disorders like cancers, chronic metabolic and neurodegenerative diseases. Inside the *Hammam*, the average temperature should be $41^0$C- $45^0$C. Mild temperature warms up the body and inducing self defense mechanism. Humid environment in *Hammam* add to heat stress by reducing the vapor pressure gradient from the skin to the environment. In context of heat stress, dehydration occurs largely as a consequence of heat stress. Increased body temperature initiates chaperone- mediated autophagy (CMA) by producing heat shock proteins. Both heat stress and dehydration display hormesis [16].

Heat stress is a widely used hormetic agent, not only because it is easy to implement and gives consistent results, but because of heat stress mainly acts through an evolutionarily highly conserved stress response pathway known as the heat shock (HS) response. HS response is one of the primordial intracellular defense mechanisms against stressful conditions in which extracellular stress (and intracellular stress from denatured proteins) initiates a series of events starting with signal transduction, activation and nuclear translocation of heat shock factors (HSF), DNA binding of heat sock factor (HSF), initiation of HS gene transcription, and preferential translation of heat shock proteins (HSPs). Which then perform various biological functions[37] [38]. A series of pilot studies performed for

testing the effects of 1 hour heat shock at different temperatures, ranging from $37^0$C to $45^0$C on synthesis of HSPs in the following 3 hr period. Maximum HSPs synthesis was observed at $43^0$C. However, at $41^0$C, HS response was about one-third of the maximum response, and so this temperature was selected for long term studies[38]. Induction of heat shock response is through the heat shock transcription factors (HSF) working as molecular links between heat stress and stress response[37, 38]. HSPs are known to play diverse roles as chaperones. In unstressed cells, HSPs act in successful folding, assembly, intracellular localization, secretion, regulation and degradation of other proteins. Under conditions in which protein folding is perturbed or proteins begin to unfold and denature, HSPs have been shown to assist in protein refolding, to protect cellular systems against protein damages, to dissolve protein aggregates to some extent, to sequester overloaded and damaged proteins to degradation, and to interfere with the apoptotic programme[37] [38] . The chaperone network assists in maintaining protein functionality and counteracts intrinsic and extrinsic forces that perturb protein folding. Hence, molecular chaperones maintain cellular, tissue, and organismal health[39] [40]. When cells are exposed to heat stress, stress proteins called HSPs are upregulated in cells, and they are thought to serve as molecular chaperones.. In addition to these well-characterized intracellular functions of HSPs, researchers have suggested that extracellular HSPs enhance immune system. The most inducible and abundant, and therefore most studied is HSP72. Although various stressors can trigger upregulation of HSP-72, thermal stress appears to be one of the most effective stressor to increase the intracellular and extracellular concentrations of HSP-72. Whole body heat stress that includes the head and face might effectively modulate cardiovascular, hormonal, and molecular chaperones. Researchers have suggested that catecholamines mediate the release of HSP-72 in response to stress [41].

**2.4. *Riyazat* (Exercise).** *Riyazat* is most common therapeutic regimen, employed in Unani Medical System. According to *buqrat* (Hippocrates) who is on restricted diet, should not do any heavy exercise because it produces fatigue. It is well known that life and health depend upon food. All foods are not digested/ metabolized properly and remain as a waste in the body and there removal is necessary for health. Wastes produce *sue-mizaj* (temperamental dys-homeostasis) in various tissues of the body by altering *akhla-e-araba* (four body humours). Thus exercise prevents the accumulation of wastes and upregulates evacuation from the body to maintain health by regulating *akhlat-e-araba* [42] [43]. Exercise affects brain predominantly. Exercise make smarter, happier and produces more neurons in the brain depending on the dose (intensity) of the exercise training. Physical activity induces pleiotropic effects for the whole organism including brain. The effects of physical exercise can be described by means of a hermetic response on cognition and mood, These effects have been closely related to the adult hippocampal neurogenesis (AHN). AHN is a phenomenon consisting of the formation of new neurons during adult life, and certainly these neurons are highly responsive to exercise. Physical activity is an essential component of everyday life. Hormetic effects of exercise on muscles, bones, immune system, cardio vascular system, and brain make the whole body healthier and resistant to further stress [44] . Heating skeletal muscles during exercise can stimulate HSP-72, thereby protecting against disuse atrophy and enhancing muscle re-growth in rats and producing hypertrophy in humans [45] .

Reactive oxygen species (ROS), heat stress produced by increased metabolism, and dehydration produced by excessive sweating are responsible for hormesis in *riyazat* (exercise). ROS are the most powerful pro-oxidant as well as hermetic agent. There is clear evidence that an acute bout of heavy exercise generates sufficient ROS to develop hormesis[46]. One of the most important findings of free radical chemistry associated with exercise was that muscle contraction can activate redox-sensitive signal transduction pathways to stimulate the expression of certain gene products that function to restore ROS homeostasis. The pathways that are sensitive to ROS include nuclear factor *kappa* B (NF*k*B) and heat shock proteins (HSPs)[47]. Activation of redox sensitive pathways usually results in gene products that would restore intracellular redox homeostasis and protection from potential oxidative stress. It has been recently shown that oral administration of antioxidants and inhibition of intracellular ROS source could adversely affect antioxidant enzyme adaptation, mitochondrial biogenesis and insulin sensitivity in animal and human skeletal muscle in response to exercise clearly demonstrating that ROS play a key role in exercise hormesis [48].

Other element of exercise related to hormesis is increased body temperature, leading to profuse sweating and the triggering of chaperone proteins (HSP-72). It is well known that heat act as a powerful hermetic agent. Researchers have reported that an increase in extracellular HSP-72 due to exercise was much greater than that due to passive heating in *hammam* [49] Dehydration associated with exercise also contribute in hermetic process. Dehydration in exercise is produced by excessive and profuse sweating. Dehydration is also acts as a hormetic agent [50].

## 2. CONCLUSIONS

Significant advances have not been made in recent years in unani system of medicine towards the understanding of the mechanisms involved in the effectiveness of non pharmacological regimens. In this review article, it is hypothesized that hermetic process is involved in the effectiveness of *Ghiza-i-tadaabeer* (dietary regimens), *hammam* (Turkish bath), and *riyazat* (exercise). More studies on human are required to prove the efficacy of these regimens in various human pathologies. In order to achieve these goals, the efforts of an array of scientists, health professionals and government agencies will be required.

**Figure.1: Hormetic mechanisms**

| Hormetic factors | Cell signaling | Hormetic effectors |
|---|---|---|
| **Ghiza-i- tadaabeer (Dietary regimens)** | Free radicals | **Antioxidants** |
| Dietary energy restriction | | |
| Dietary phytochemicals | Energy depletion | **Protein chaperones** |
| **Hammam (Turkish bath)** | | |
| Heat stress | **Transcription factors** | **Growth factors** |
| Dehaydration | Nrf-2 | |
| **Riyazat(Exercise)** | NF-kB | **Mitochondrial proteins** |
| Heat stress | | |
| dehydration | | |

## REFERENCES


1.Azmi A A, Basic concepts of unani medicine, Jamia Hamdard, New Delhi,1995.

2.Melzer K, et al; Physical activity: The health benefits outweigh the risk. Curr Opin Nutr Metab Care; 2004; 7; 641-647

3.Mark P. Mattson;Dietary factors, Hormesis and Health; Aging Research Reviews;2008 January,7(1):43-48

4.Calabrese EJ et al 2007, biological stress response terminology: integerating the concepts of adaptive response and preconditioning stress within a hormetic dose response framework. Toxicol. Appl. Pharmacol. 222: 122-128

5.Suresh I.S. Rattan; Hormetic modulation of aging and longevity by mild heat; Dose response, 3: 533-546, 2005 [doi: 10:2203/ dose response. 003.04.008]

6.Qiang Zhang, Jigbopi et al; Hrmesis and adaptive cellular control systems;dose-response;6:196-208,2008[doi:10.2203/dose-response.07-028.Zhang]

7.Mattson MP et al.,Excitotoxic and excitoprotective mechanisms: abundant targets for the prevention and treatment of meurodegenerative disorders., Neuromolecular medicine 2003;3:65-94 [Pub Med:12728191]

8. Mattson MP , Hormesis defind; Ageing Res Rev. 2008; January; 7(1) : 1-7

9.Mathars J et al., Antioxidant and cytoprotective responses to redox stress. Biochem Soc Symp, 2004, 71 : 157-176 [Pub Med:15777020]

10.Yellow DM et al. Preconditioning of the myocardium: from cellular physiology to clinical cardiology. Physiol Rev 2003; 83:1113-1151, [Pub Med:14506302]

11.Sollot S ; Conditioning ischemia hormesis, Aging RES Rev, 2007

12.Li F et al, Heat stress prevents mitochondrial injury in ATP – depleted renal epthelial cells, Am J Pyhsiol, 2002;283: C 917-926.[Pub Med:12176748]

13.Korde A Set al,. The mitochondrial uncoupler 2,4- dinitrophenol attenuates tissue damage and improves mitochondrial homeostasis following transient focal cereberal ischemia; J Neurochemistry 2005; 94 : 1676- 1684. [ Pumb Med: 16045446]

14.Matson MP; Diet induced hormesis and longevity; Agin Res Rev; 2007

15. Mattson MP , Cheng A; neurohormetic phytochemicals: low dose toxins that induce adaptive neuronal stress responses; trends neuroscience 2006; 29: 632-639.[ Pub Med:17000014]

16.Ibne sina: Alqanoon-fil-tib, 2nd edition, Pasha Mazhar H,translator. Karachi, Pakistan: Inter Services press; 1998,pp. 408-425.

17.Ammar ibne Anwar and Mohd Usman: A Contemporary Review of Dietetics Contemplating Abu Bakr Muhammad Ibne Zakariya Al Razi Perspective; Journal of Integrated Community Health 2020; vol.9(1), 17-20

18.Hamdani MK. Usool e tib: Aligarh: Syed Mohammad Kamaluddin Hamdani, Muslim University; 1980: 139,168,169,271,299-300, 425-428

19.Modanlou HD. Tribute to Zakriya Razi (865-925AD), an iranian pioneer scholar. Arch Iran Med 2008; 11: 673-677

20.Mark P. Mattson; Dietary factors, Hormesis and health; Ageing Res Rev. 2008; 7(1): 43-48

21.Bruce- Keller AJ, Umberger G, Mc Fall R, Mattson MP. Food restriction reduces brain damage and improves bahavioral outcome following excitotoxic and metabolic syndrome. Ann Neuro 1999; 45:8-15.[ Pub Med:9894871]

22. Johnson JB, Summer W, Cutler RG, Martin B, Hyun DH, Dixit BD, Pearson M, Nassar M,Tellejohon R, Maudsley S, Carlson O, John S, Laub DR, Mattson MP. Alternate day calorie restriction improves clinical findings and reduces the markers of oxidative stress and inflammation in overweight adults with moderate asthma. Free Radic Biol Med 2007;42: 665-674.[Pub Med:17291990]

23.Yu ZF, Mattson MP . Dietary restriction and 2- deoxyglucose administration reduce focal ischemic brain damage and improve behavioral outcome: evidence for a preconditioning mechanism. J Neurosci Res 1999; 57:830-839 [Pub Med: 10467254]

24. Fernandes G, Yunis EJ, Good RA. Influence of diet on survival of mice. Proc Natl Acad Sci USA 1976; 73:1279-1283.[ Pub Med]

25.Heydari AR, Wu B, Takahashi R, Richardson A.Expressions of heat shock protein 70 is altered by age and diet at the level of transcription. Mol Cell Biol 1993; 13:2909-2918.[Pub Med:7682654]

26.Hyun DH, Emerson SS, JO dg, Mttson MP, de Cabo R. Calorie restriction upregulates the plasma membrane redox system in brain cells an suppresses oxidative stress during aging. Pro Natl Acad Sci USA 2006; 103:19908-19912.[Pub Med:17167053]

27. Tae Gen Son, Simonetta Camandola, Mark P Mattson. Hormetic Dietary Phytochemicals. Neuromolecular Medicine. 2008:10(4):236-246.[doi:10.1007/s12017-008-8037-y]

28.Norman AW.2008. From vitamin D to hormone D:fundamentals of vitamin D, endocrine system, essential for good health. Am J Clin Nutr 88(suppl):491S-499S.

29.Aubin JE and Heersche JNM. 1997. Vitamin D and osteoblasts. In: Feldman D,Glorieux FH, Pike JW(eds), vitamin D, pp313-328. Acad press, Sandiago.

30. Daniel P. Hayes. Nutritional Hormesis and Aging.Dose-Response,8:10-15,2010[DOI:10.2203/dose-respnse.09-012.Hayes]

31. Hayes DP. 2005. The protective role of fruits and vegetables against radiation- induced cancer. Nutr Res 63: 303-311

32. Miura Y, Chiba T, Tomita I, et al. Tea Catechins prevent the development of atherosclerosis in apoprotein E- deficient mice. J Nutr 2001; 131: 27-32[Pub Med:11208934]

33.Wu CC, Hsu MC et al. Upregulation of emeoxygenase -1 by Epigallocatechin-3- gallate via the phosphatidylinositol 3 kinase/Akt and ERK pathways. Life Sci 2006; 78:2889-2897. [pub Med:16378625]

34. Mohammadi,K.; Thomspson K.H.; Patric B.O.; Storr, T.;et al.; Synthesis and characterization of dual function vanadyl, gallium, and indium curcumin complexes for medicinal applications. J Inorg Biochem 2005: 99 (11), 2217-25

35. Scapigini G, Colombrita C, Amadio M, D Agata V,et al. Curcumin activates defensive genes and protects neurons against oxidative stress, Antioxid redox signal 2006; 8:395-403.[Pub Med16677086]

36.B Juhasz et al. Hormetic response of resveratrol against cardioprotection .Exp Clin Cardiol; vol 15(4); 2010

37. Kiang JG et al. 2003. Heat stress. In:Tsokos GC, and Atkins JL (ed), combat medicine: Basic and clinical research and emergency medicine. 83-101 pp.Humana press. New Jersy.

38.Suresh I.S. Rattan. Hormetic modulation of aging ang longevity by mild heat stress. Dose-response, 3:533-546, 2005 [doi: 10.2203/ dose-response. 003.04.008]

39. Brandvold, K.R., and Morimoto, R.I (2015). The chemical biology of molecular chaperones-implications for modulation of proteostasis. J. Mol. Biol.. 11, 2931-2947. [Doi: 10. 1016/j.jmb.2015.05.010]

40.Zohar Bromberg and Yoram Weiss. The role of the membrane- initiated heat shock response in cancer.Front. Mol. Biosc., 2016[doi.org/10.3389/fmolb.2016.00012]

41.Masaki Iguchi; Andrew E. Littmann; Shuo-Hsiu, et al., Heat stress and cardiovascular, Hormonal, and heat shock proteins in humans, Journal of Atheletic training. 2020; 47 (2) : 184-190.

42.Ibne sina. Kulliyat Qanoon.2006. New Delhi: Eijaz Publishing House;

43.Ibne Sina 2010. Al Qanoon Fil Tib. New Delhi. Idara Kitabushifa.production.

44.Simona Gradari, Anna Palle, Kerry R. Mc Greevy, Angela Fontan, Lozano and Jose L. Trego. Can exercise make you smarter, happier, and have more neurons? A hormetic perspective . Frontiers in neuroscience. Neurogenesis. 2016 [doi. org/10. 3389/ fnins. 2016.00093]

45. Goto K. Responses of muscle mass, strength and gene transcripts to long term heat stress in healthy human subjects. Eur J Appl Physiol 2011; 111: 17-27; PMID : 20803152; [dx. Doi.org/10.1007/s00421-006-0331-5]

46. Powers SK et al. 2008. Exercise induced oxidative stress: Cellular mechanisms and impact on muscle force ; Physiol Review; 88 (4) : 1243-76.

47.Good year LJ. 1996. Effects of exercise and insulin on mitogen- activated protein kinase signaling pathways in rat skeletal muscle. Am J Physiol. 271 (2) : E 403-8.

48. Allen RG, Tresini M 200. Oxidative stress and gene regulation. Free radical Biol Med. 28(3) : 463-99.

49.Gomez-Caberra MC, et al. 2008. Oral administration of vitamin C decreases muscle mitochondrial biogenesis and hampers training induced adaptations in indurance performance. American journal of clinical nutrition. 87 (1) : 142-9.

50. Withan M et al. Effects of exercise with and without a thermal clamp on the plasma heat shock proteins 72 response. J. Appl. Physiol. 2007; 103 (4) : 1251-1256.