



Traditional Persian Medicine and Autophagy: Integrating Ancient Health Principles with Modern Cellular Mechanisms

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Abstract

Autophagy, a cellular process responsible for maintaining cellular homeostasis through the degradation and recycling of intracellular components, has a complex relationship with various human diseases, including cancer, neurodegenerative disorders, and infections. Traditional Persian Medicine (TPM), with a 10,000-year history, emphasizes health preservation through six essential principles: physical activity, nutrition, sleep, psychological well-being, air quality, and the excretion of body waste. This review examines the intersection of these principles with autophagy, highlighting the potential of TPM in modern health practices. Recent studies have shown that physical activity induces autophagy, aiding in the prevention and treatment of diseases such as Alzheimer's and diabetes. Nutritional management, another key TPM principle, influences autophagy through practices like intermittent fasting, which can improve insulin sensitivity and prolong life. Sleep, critical for bodily functions and waste disposal, affects autophagy, with disruptions linked to conditions like sleep apnea and cardiovascular diseases. Excretion and retention of

necessary materials are crucial for health, with autophagy playing a role in managing obesity, renal function, and gastrointestinal health. Clean air is essential for well-being, and studies indicate that air pollution can stimulate autophagy, potentially leading to liver steatosis. Psychological states also significantly impact autophagy, with stress and emotional well-being influencing cellular processes. This review suggests that the non-pharmacologic modulators of autophagy inherent in TPM's six essential principles could precede pharmaceutical interventions due to their simplicity, safety, and affordability. Health authorities are encouraged to consider these principles in policies for disease treatment and health improvement, leveraging the potential of autophagy modulation for better health outcomes.

Keywords: Autophagy, Traditional Persian Medicine, Health Preservation, Disease Treatment, Six Essential Principles, lifestyle medicine

Introduction

Autophagy is a cellular process, which is responsible for maintaining cellular homeostasis. It involves the degradation and recycling of intracellular components, together with superfluous

Significance | Explores autophagy's role in Traditional Persian Medicine's health principles, highlighting non-pharmacologic disease treatment and prevention methods.

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and dysfunctional proteins and organelles. Recent studies have highlighted the complex relationship between autophagy and various human diseases. For example, it plays a significant role in cancer, neurodegenerative disorders and infectious diseases (Ghavami et al., 2022; Lei & Klionsky, 2021). Traditional Persian Medicine (TPM) with a 10000-year history, is a rich and health-centered medical school. (Elgood, 2010; Sadeghi et al., 2020; Sajedeh Ghasempour, 2024). Medicine was a kind of job which preserved the human health and revitalized the individual by science and practice. The physicians and scientists of this school have always considered and emphasized health preservation as the first duty of a physician (Bokhari, 1992; Naseri & Ardakani, 2004; Khodaie et al., 2021). Since the establishment of the World Health Organization (WHO) in 1946, it has worked on the basis of the slogan of "Prevention is better than the treatment" and has annually chosen a common health problem in the world as its slogan and has aimed to solve it by efforts and plans (Naseri, 2004). The TPM explains principles of health preservation from the beginning, classifies it into essential and non-essential principles, expresses its importance, and states six essential principles of healthy life, i.e., physical activity; nutrition and dietary habits; sleep and awareness; psychological feature; air and climate; and excretion of body waste and retention of the necessary material (Avicenna, 2005). From the perspective of Avicenna, the priority of these principles begins to preserve health by sport: The most considerable measure for the health preservation is someone who exercises, and then food and sleep measures. The rich school goes beyond this issue and claims that the above measures are prior to drugs even in the treatment, and the food measures are in the first place of importance in the treatment procedure. "Certainly, the treatment becomes complete by three things: first, the nutrition measure; second, the medication, and third, the application of manual practice" (Avicenna, 2005). If a person's measures of six essential principles are right, the body is able to manage vital activities by regulating and applying intelligent natural forces. These activities generally include digestion of food and its delivery to organs, and then excreting and disposing the waste from organs leading to intracellular cleansing and replacement of intracellular matters. This intelligent intracellular activity is interpreted as "autophagy" (Nozad et al., 2016). Given the importance of six essential principles in the TPM and the importance of autophagy in new studies, the present study sought to describe the roles of six essential principles in health preservation and disease treatment in terms of autophagy (Figure 1).

Methodology

The present study is a review study that first investigates the autophagy mechanism and then its effect on the health preservation and disease treatment based on modern medical studies.

Given that the traditional Iranian medicine has considered especial importance for observing six essential principles in the health preservation and disease treatment, the relationship between each principle with autophagy was reviewed based on new studies after extracting the principles from traditional medicine sources in Iran. Besides, the sequence of six essential principles was according to the mentioned importance in the traditional medicine sources.

Autophagy and its mechanisms

Autophagy is a Greek word that consists of two parts, *auto* with the meaning of "self" and *phagy* with the meaning of "eating" (this term was first used by Christian de Duve). In the early years, most studies considered the morphology of lysosomes, but genes associated with autophagy and the molecular system of autophagy control were detected in yeast and then human by Osion et al. in 1990 leading to a major step in understanding the importance of autophagy in human health and diseases (Sarmah et al., 2021; Yang & Klionsky, 2010). Autophagy in fact is a process in which cells purposely purify their cytoplasmic components (Ghavami et al., 2022; Klionsky, 2004), and it plays an important adaptive role in preserving organisms against various pathologies such as infections, cancers, aging and diseases or, in other words, it is as a cellular response to these stresses. Autophagy functions may be harmful in some circumstances (Lei & Klionsky, 2021; Levine & Kroemer, 2008). Despite the fact that researchers thought that autophagy was only an intracellular decomposing process and called it self-eating, it has now been proven that the self-eating is just one of autophagy goals; and other important processes such as the biosynthesis process (the cvt pathway), prevention of disease and aging (through removal of damaged organs), regulation of metabolism (by eliminating certain enzymes), as well as more advanced pathways such as the death of sympathetic neurons depend on autophagy (Klionsky, 2004). Chaperone-Mediated Autophagy (CMA), microautophagy, and macroautophagy are different in terms of physiological functions and the way of connecting load to lysosomes (Levine & Kroemer, 2008). A kinase signal network regulates the onset of autophagy, but Ulk1/Atg1 has a key kinase signal at the beginning of autophagy. Various types of autophagy, which are selectively performed include Mitophagy (autophagy that is done by mediation of mitochondria); Crinophagy (autophagy of granules); Aggrephagy (autophagy of intracellular accumulated proteins); ER-Phagy (Selective autophagy of endoplasmic network); PMN/Micronucleophagy (Micro-autophagy of components in the core); Pexophagy (Selective autophagy of peroxisomes); and Xenophagy (Intracellular autophagy of pathogens and phagosomes) (Gottlieb, 2012). The traditional Iranian medicine introduces six essential principles of health preservation and disease treatment, and these six principles are prioritized according to the importance (Avicenna, 2005; Rezaeizadeh et al., 2009).

Physical activity and autophagy

Physical activity and exercise are the first strategies for health preservation in the traditional Iranian medicine school, and due to its utmost importance, Avicenna stated it as follows: By exercise, you will not need any treatment. (Avicenna, 2005). Recent studies have focused on the effects of exercise through the induction of autophagy in the prevention and treatment of diseases. Exercise can dramatically affect body cleansing and health preservation through stimulation of autophagy in various organs of the body such as muscles, liver, pancreas and fatty tissues that play vital roles in regulating body metabolism (He et al., 2012). According to an animal study on mice, exercise can reduce sedimentation of β -amyloid in hippocampal cells by induction of autophagy, and thus affects the prevention and treatment of Alzheimer's disease (Zhao et al., 2018). An interventional study on 30 men with type 2 diabetes indicated that exercise could improve the functions of beta cells and also improve insulin sensitivity, thereby decreasing blood glucose levels (Eizadi et al., 2012). In a study on Alzheimer's mice with Ps2m gene mutation, it was found that exercise can improve the metabolism of energy in skeletal muscle cells by reducing sedimentation of β -amyloid in those cells. Therefore, exercise can be suggested as a therapeutic strategy for skeletal muscle disorders in Alzheimer's patients (Yook & Cho, 2017). Awer et al. found that endurance exercise could increase autophagy in muscle cells by increasing the transcription of the genes associated with autophagy (Jamart et al., 2012). In another study, exercise with an autophagy mechanism in aging could prevent cardiovascular diseases, osteoporosis, diabetes, sarcopenia, and depression (de Cabo et al., 2014).

Autophagy and food

According to Avicenna, food management is the second essential principle of health preservation and preventing diseases after exercise. In the Iranian medicine, food management plays an important role not only in the health preservation, but also in the disease treatment (Avicenna, 2005). Muhammad ibn Zakariya al-Razi, a well-known physician in the 3rd and 4th centuries, believed that "As long as the physicians can, they should treat patients with nutritional measures and not prescribe medication" (Razi M., 1430 AH.). The use of food in the prevention and treatment of diseases has been highly considered by the world's scientific community. According to a study, garlic as a nutrient can cause cancer cells to die through apoptosis and autophagy induction (Chu et al., 2013). According to Mostafavi Kashani, a contemporary scholar, among various medical schools, the ones with the highest potential for health preservation and disease treatment by food are superior (Mostafavi Kashani SJ, 1979.). In the Iranian medicine, food management is determined by the temperament of food and people

as well as food quantity. There are four states in the field of food quantity: fasting, food restrictions, food modulation and increase that vary from one person to another (Avicenna, 2005). According to a study, the role of nutrition has become more evident through the induction of autophagy in health preservation and various diseases. Intermittent food dietary increases insulin sensitivity and the resistance of brain neurons to toxic stress, reduces the incidence of illness and prolongs life. Other research results indicated that food reduction could help eliminate waste in the body through the pathway of cellular autophagy (Nozad et al., 2016). New studies have found a significant relationship between autophagy and obesity indicating that autophagy regulation can play an important role by controlling the intake of food, fat cells, beta-cell function, insulin sensitivity and hepatic steatosis in obesity (Lavallard et al., 2012). Autophagy is an excellent cellular pathway for progression, differentiation, survival and homeostasis and can play a protective role against aging and some pathologies such as cancer, heart disease and infections. Lifestyle changes intervention in aging decreases blood lipids, blood pressure, improves heart rate and fat profiles by limiting calories.

Furthermore, the starvation strategy increases life, decreases blood pressure and other metabolic syndromes, improves oral memory, reduces the aging phenomenon, prevents overweight and decreases weight in obese people. By strengthening stress resistance and reducing the function of cellular mitochondria in aging (such as the production of free radicals, increased calorie intake, chronic hyperglycemia, and fat accumulation), the autophagy applies its preventive effect. Compared to metformin, rapamycin, spermidine and resveratrol drugs, the intervention of lifestyle changes in humans has also been effective in the induction of autophagy in rats (de Cabo et al., 2014). Due to the hunger, autophagy affects oogenesis activities both in germ and follicular cells in common fruit flies. In a study, the elimination of food for common fruit flies resulted in the autophagy in fatty organs and also influenced the size and structure of their ovary. In fact, the regulatory role of autophagy by increasing germ cells leads to an increase in the range of reproductive activity (Barth et al., 2011). A review study by Hejri Zarifi et al. indicated that hunger and calorie intake are strong non-genetic autophagy stimuli that can be an alternative approach compared with intervention medications for induction of autophagy due to its simplicity, safety and affordability and the reduction of unwanted side effects (Zarifi, 2018).

Autophagy and sleep

Sleep management is the third most important principle of health preservation and disease treatment in the traditional Iranian medicine (Avicenna, 2005; Bahaeddin et al., 2023). According to Iranian traditional medicine sources, enough sleep improves food digestion and organ functions and is very effective in waste disposal

and body cleansing. Sleeping can thus result in better functioning of body organs (kidney, liver, heart, brain, lung, etc.). Any changes in the quality and quantity of sleep patterns can damage health and cause serious illness in the body. Despite the fact that sleep is in the third place of the health preservation principles after exercise and nutrition, it is prescribed before medication in the management of patient treatment, indicating the importance of sleep in the treatment of diseases in the traditional Iranian medicine. However, excessive sleep makes the body lethargic, and staying awake generates heat in the body owing to the high frequency metabolic activities and extra calories are burnt away. Thus, a balance between excessive sleep and staying awake is a must to preserve health (Rezaeizadeh et al., 2009; Shayesteh et al., 2020). New studies have indicated that sleep apnea can cause disturbance in the induction of autophagy and apoptosis in hippocampal cells by the creation of oxidative stress such as GRP78/ Bip, PERK, CHOP, and thus disrupts spatial memory of mice. Those studies found that feeding a solution containing *Lycium Barbarum* Polysaccharides two hours before hypoxia can play a neuroprotective role in hippocampal cells (Lam et al., 2015). In another animal study, chronic discontinued hypoxia in sleep apnea not only damaged renal tubular cells, but also activated autophagy in epithelial cells of tubule, which may even contribute to damaging tubular cells (Liu et al., 2018). The created hypoxia in sleep apnea causes disruption of airway muscle activity. In a study on *Genioglossus* muscle cells, which were made of stem cells, the sustained hypoxia could lead to muscle dysfunction by induction of autophagy (D. Zhang et al., 2018). Many studies have found that autophagy is induced in various cardiovascular diseases, which increases patient survival, but much of it can cause abnormalities. The created alternating hypoxia in sleep apnea syndrome improves the contractile function of myocardial cells in mice with heart failure by the induction of autophagy, and the inhibition of autophagy causes necrosis of monocytes, and thus systolic dysfunction in them (Maeda et al., 2013). According to an animal study on mice, sleep deprivation causes muscle atrophy by increasing Corticosterone levels and, in parallel, growing autophagic proteins such as LC3 and P62/SQSTM1 (Mônico-Neto et al., 2015). Many studies have indicated a close relationship between sleep disorders and Multiple Sclerosis (MS) disease; for instance, Gosalipour et al. conducted a research and found that PER3 gene disorder (from responsible genes in controlling sleep rhythm) could increase the risk of MS (Gosalipour et al., 2017). In another study, they found that autophagy moderated T cells through gene-5 and could play an active role in the relapse and prevention of MS (Alirezaei et al., 2009).

Autophagy, excretion of body waste and retention of the necessary material

Maintaining and protecting the necessary body matters (such as blood and nutrients) and the disposal of waste and poison from the body through the right ways and natural pathways are other essential principles of health preservation and treatment of disease (Avicenna, 2005). Vomiting in TPM means purifying and evacuating the body from abnormal and additional waste. Retention of nutrition agents inside the body and excretion of waste products are important for its sustenance. Any alteration or variation in this process can lead to many types of diseases (Naseri & Ardakani, 2004; Nozad et al., 2016). Etiological studies of the past three decades have found that obesity is due to an imbalance in energy and a disorder in the neurohormonal regulatory system, and both of them are strongly regulated by autophagy. The lack of autophagy homeostasis in fat tissue causes an adverse effect on local and global metabolisms leading to the promotion of metabolic abnormalities (Y. Zhang et al., 2018). Autophagy is a potent regulator of adipose tissues in obese people, especially in the omentum, due to its degree of obesity, and can lead to degeneration of visceral fat and hypertrophy of adipocytes (Kovsan et al., 2011). Urine is an excreted substance, and its retention or disorder in its disposal is associated with severe and rapid complications. This disorder can be due to mechanical obstruction (such as stone) or functional obstruction that ultimately leads to damage to renal tubules. Renal ischemia-reperfusion injury leads to autophagy through light chain3, beclin-1 and p62 levels and an increase in autophagic vacuoles and induction of apoptosis (Zhang et al., 2015). Constipation is a common gastrointestinal tract disease that is commonly known as the "mother of diseases" in the traditional Iranian medicine (Yaghoubi et al., 2017). Stool stagnation is a major factor in colon cancer, appendix, and inflammatory bowel diseases of the bladder (Bharucha et al., 2005). In a study on patients who were hospitalized for more than two weeks, constipation increased the risk of death in stroke patients by 6.8% (Ingeman et al., 2011). Reduction of the passage of matters from the intestines or excretion disorder can be due to certain diseases such as diabetes, hypothyroidism, improper digestion of food, some antihypertensive drugs or lipid-lowering drugs (Locke III et al., 2000). In addition, chronic habitual constipation and inappropriate carbohydrate diet have significantly increased the prevalence of this disease. Correcting the stool disposal (reducing or not using the European or Western waters closet, WC/EWC, versus squat toilets) (Yaghoubi et al., 2017) and inducing autophagy by changing lifestyles and modifying diets to reduce constipation can be effective in reducing the incidence and complications of constipation (de Cabo et al., 2014). Polycystic ovary syndrome (PCOS) is a common cause of infertility due to the lack of ovulation because of an imbalance in vomiting and congestion. According to research on roles of enzymes in the collagen decomposition of the surrounding tissue of follicles in the PCOD, a decrease in matrix

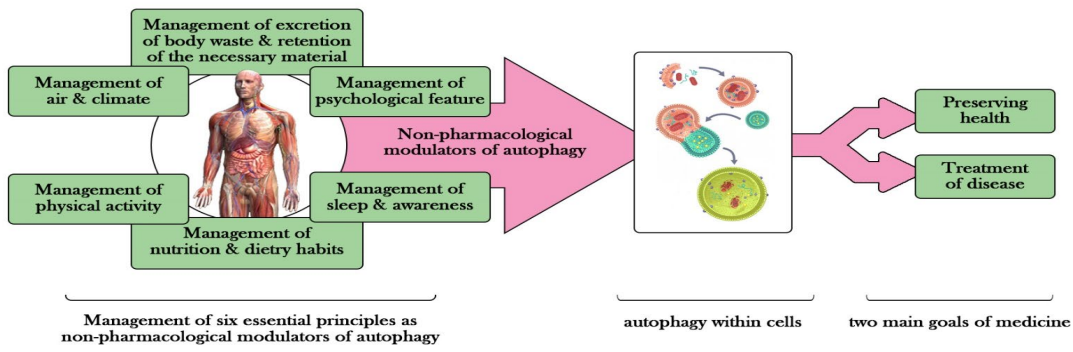


Figure 1. Six essential principles and autophagy: According to TPM, the goal of medicine is to preserve health and to treat diseases and the first step to achieve these two goals is to adhere to these principles.

metalloproteinase activity (MMP-2) and an increase in the expression of Lysyl oxidase (LOX) in the ovarian connective tissue may be the cause of PCOD cytogenesis. Therefore, an increase in apoptosis in these patients can have an effective therapeutic (Endo et al., 2001). Non-appearance of menstruation, which is called the amenorrhea and oligomenorrhea in the modern medicine, is a common menstrual disorder in the world and can have numerous complications on organs such as the brain, respiratory system, and uterus according to the teachings of the traditional Iranian medicine (Arani MT, 2014). This disorder can lead to other pathological conditions such as infertility, reduced fertility, malignancy, cardiovascular diseases, diabetes, hirsutism and acne in young girls and women and poses a threat to the general health of this group (Agarwal & Venkat, 2009).

Air and autophagy

Air/climate is the fifth principle essential for the health preservation and disease treatment (Avicenna, 2005). The traditional medicine sources call the water and air pollution as the "Cholera" pollution, and consider three active factors in this kind of pollution. Fresh and clean air is essential for good health, conversely, polluted air can weaken the body and makes it more vulnerable to diseases. Avicenna considers air as the essential substance for body and soul (energy): "Air is the essential substance for body and soul" (Avicenna, 2005; Babaeian et al., 2016). Recent studies indicate that air pollution can increase the risk of metabolic syndrome. In an animal study on mice, it was found that air pollution stimulated autophagy in rat liver cells and subsequently contributed to the liver steatosis (Qiu et al., 2017). This finding may be a reason for justifying the prevalence of fatty liver in current industrial societies. A review study indicated that various stimuli such as air pollution, cigarette smoke, hypoxia, microbes, inflammation and ischemia, drugs such as Bleomycin and inhalation of pollen could activate autophagy in pulmonary cells. Hence, autophagy can be considered as a chief modulator of pulmonary diseases and a therapeutic potential (Aggarwal et al., 2016). Finally, according to a recent study, the measured levels of autophagy in Peripheral Blood Mononuclear Cells (PBMCs) of the Chronic Obstructive Pulmonary Disease (COPD) patients, can play a biomarker role in the exacerbation of COPD and can be a goal in the COPD recovery (Wu et al., 2018).

Psychologic features and autophagy

According to TPM various mental states such as anger, fear, pleasure and happiness can have a profound effect on temperament of the body and as a result human health (Avicenna, 2005). In the Iranian medicine, it is important to pay attention to mental and emotional states of people, as Avicenna states in his book, The Canon of Medicine, "A good and beneficial treatment that enhances

the animal and worldly soul, like vitality, is meeting people with whom we are intimate and become happy to see them, but we are prohibited from communication with those who make us ashamed and also banned from harmful things" (Avicenna, 2005). Hippocrates, often referred to as the "Father of Medicine", says that "some patients, even if their conditions are dangerous, can easily regain their health by relying on the kindness of physicians" (Jacques Jouanna & Van der Eijk, 2012; Miles, 2005). Sayyed Isma'il ibn Husayn Gorgani, a Persian physician of the 5th and 6th centuries, states that "the effect of psychological states in people is greater and faster than eating and drinking, and other essential principles of life" (Abivardi, 2001; Ardekani, 2005). Types of mental states include wrath, joy, impatience, sadness, grief and shyness each of which have an individual temperament that causes balance in the main temperament of human and make changes in the human society (Rezaeizadeh et al., 2009; Shayesteh et al., 2020). New studies have also clarified the impact of mental health and illness. For instance, an animal study on mice indicated that the isolation of baby mice from mothers caused anxiety and depression in them. In a study on the mechanism of these behavioral disorders in mice, mothers' separation led to a different autophagic response in hippocampal cells and prefrontal cortex cells (PFCs) (the autophagic induction was seen in the hippocampus of autophagy inhibition and PFCs induction), and this state can be related to the signal path of NR2B (Liu et al., 2018). A study indicated that the autophagy regulation played a role in the pathogenesis of the Major Depressive Disorder (MDD), the mechanism of activity of some antidepressants, and also, its regulation in neurons can be effective in the development of therapeutic interventions in patients with the MDD (Jia & Le, 2015).

Eventually, researchers have found that the autophagy disorder is effective in the pathogenesis of schizophrenia and can also predispose individuals to mood disorders, psychotic symptoms, and behavioral changes (Schneider et al., 2016). Prenatal stress (PS) plays a significant role in causing complications such as anxiety, depression and cognitive impairment in children. In an animal study on mice, it was found that the PS significantly increased the level of autophagy in the children's hippocampal cells, and the autophagy regulation could reduce the severity of degeneration caused by PS in children (Zhang et al., 2017).

Conclusions

Autophagy is a physiological process that can empower cells against stress by engaging cytoplasmic components. Even though the excessive or lower activity of autophagy can be harmful to cells, autophagy modification has beneficial effects on the treatment of many diseases. In this regard, it seems that non-pharmacologic modulators may precede pharmaceutical interventions in inducing autophagy due to their simplicity, safety and affordability. The

traditional Iranian medicine considers six essential principles as the priorities in health preservation and disease treatment. According to this review study, all of the six principles can be natural factors for modifying autophagy and play crucial roles in preventing and treating diseases. Therefore, we suggest health authorities consider these principles as policies on disease treatment and health improvement.

Author contributions

R.V. and K.A. conceived the study and developed the hypothesis. R.P. and M.J.M. contributed to data collection and performed the initial analysis. M.N. and S.F.J. led the data interpretation, manuscript writing, and final revisions. All authors read and approved the final manuscript.

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Competing financial interests

The authors have no conflict of interest.

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