



## Mini Review Article

### Anorexia: Highlights in Traditional Persian medicine and conventional medicine

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#### Abstract

**Objective:** Anorexia and impaired appetite (Dysorexia) are common symptoms with varying causes, and often need no serious medical intervention. Anorexia nervosa (AN) is a chronic psychiatric disease with a high mortality rate. In Traditional Persian Medicine (TPM), anorexia is a condition in which anorexic patients lose appetite due to dystemperament. This review aims to discuss the common points of traditional and conventional approaches rather than introducing Persian medical recommendations suitable for nowadays use.

**Materials and Methods:** For this purpose, Avicenna's Canon of Medicine, main TPM resources and important databases were reviewed using the related keywords.

**Results:** Despite complex hormonal explanation, etiology of AN in conventional approach is not completely understood. In TPM approach, the etiology and recommended interventions are thoroughly defined based on humoral pathophysiology. In TPM approach, disease states are regarded as the result of imbalances in organs' temperament and humors. In anorexia with simple dystemperament, the physician should attempt to balance the temperament using foods and medicaments which have opposite quality of temperament. Lifestyle, spiritual diseases (neuro – psychological) and gastrointestinal worms are the other causes for reducing appetite. Also, medicines and foods with warm temperaments (such as Pea soup and Mustard) are useful for these patients (cold temperament).

**Conclusion:** Although the pathophysiology of AN in TPM is different in comparison with conventional views, TPM criteria for treatment this disorder is similar to those of current medicine. Recommending to have spiritual support and a healthy lifestyle are common in both views. Simple safe interventions recommended by TPM may be considered as alternative medical modalities after being confirmed by well-designed clinical trials.

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## Introduction

Anorexia and impaired appetite (Dysorexia) are common symptoms with varying causes, and often need no serious medical intervention (Godart et al., 2012; Shayeghian et al., 2011). Eating disorders are different entities and need to be diagnosed and treated thoroughly. According to DSM (Diagnostic and Statistical Manual of Mental Disorders)-IV criteria, eating disorders include Anorexia Nervosa (AN) and Bulimia Nervosa (BN). Formerly, AN was divided into two subtypes namely, restrictive (ANR) and binge eating/purging (ANBP) (Hanachi et al., 2013). In DSM-V, ANBP is considered as a new entity (Heaner and Walsh, 2013). According to DSM-IV criteria for diagnosis of AN, the patient, due to an intense fear of becoming fat, receives fewer calories than daily requirements in order to lose weight. A weight of  $\leq 85\%$  of what expected, dehydration and extreme thinness as well as susceptibility to digestive disorders, urinary tract disorders, heart disease and even death in severe cases, are other criteria (Fauci, 2008; Godart et al., 2012).

AN is a chronic psychiatric disease with a high mortality rate (Gentile et al., 2010; Ramoz et al., 2012). Female patients usually have a BMI  $< 17.5$  and develop low mineral bone density mass, amenorrhea, and behavioral abnormalities. Sometimes, people suffering from AN believe that they are too fat (Madsen et al., 2013). In AN, hormonal changes are resulted from starvation. In fact, an unknown mental problem results in the incidence of AN (Sodersten et al., 2008). Apparently, social relations and psychological condition of the patients are disturbed in AN (Oldershaw et al., 2011). Difficulties in the regulation of emotions probably contribute to the development of AN (Brockmeyer et al., 2012).

There are valuable medical experiences of Iranian sages and physicians mentioned in traditional Persian medicine (TPM), a school based on humoral medicine, that

may be helpful as safe and simple alternative treatments for anorexia. Besides, TPM medical terminology and diagnostic approach is different from those of modern approach. In this regard, reviewing TPM sages' viewpoints on anorexia may open a new window in the field of medical interventions for anorectic patients.

According to TPM, anorexia is a disease state in which anorexic patients lose appetite due to dystemperament (*sue-e-meza*). In TPM approaches, each individual has a peculiar temperament (*meza*) called "*mezaje-e-sehhi*" (which exerts the best functionality). *Meza* (mixing) as a medical term, practically deals with four qualities namely, warmness, coldness, wetness and dryness. Coldness and warmness are active qualities, whereas dryness and wetness are passive qualities. Combinations of active and passive qualities produce the temperament of each organ in the body. In diseases, the basic temperament turns to unwanted condition. In anorexia, *meza* of one or more organs is disturbed. For example, if *meza* of stomach tends to wetness, the appetite is diminished (Nimrouzi et al., 2014; Nimrouzi and Zare, 2014).

TPM sages had a different approach to the definition and pathophysiology of anorexia. They believed that disease states were results of imbalances in organs' temperament and humors (phlegm, sanguine, bile and black bile). Thus, treatment should focus on fixing the imbalance. TPM has mentioned six main factor that affect the health including air, diet and drink, sleeping and being awake, move and inertia, retention and release, and finally mental status (Nimrouzi and Zarshenas, 2015a). Considering these items, the health of a body and related organs remains perfect.

In the current study, we are about to review the pathophysiology, diagnosis and treatment of eating disorders, focusing on AN in TPM beside those of the

conventional medicine. Simple safe interventions recommended by TPM may be considered as alternative medical modalities after being confirmed by well-designed clinical trials.

## Methods

To start the review, the main TPM sources from the 10<sup>th</sup> to the 18<sup>th</sup> centuries were selected. The related sources were searched using the Persian keywords “*shahvat-e-ta'am*”, “*joo-e-kalbi*” and “*joo-al-baghar*”. In this regard, Avicenna's Canon of Medicine (from the 10<sup>th</sup> and the 11<sup>th</sup> centuries) (Mousavi et al., 2016), “*al-Aghraz al-tibbiyah*” (medical objectives) and “*Zakhīrah-i Khvārazm'Shāhī*” (*The Treasure of Khvarazm' Shah*) by Ismā'īl Ibn Muhammad al-husayn al-Jurjānī (from the 12<sup>th</sup> century) (Jorjani S., 1997; Zarshenas et al., 2012), “*Tibb al-Akbar*” (Akbar's medicine) and a handbook of medicine for beginners or “*Mizan al-tip*” (Shāh Arzānī) by Arzānī Muḥammad Akbar (from the 18<sup>th</sup> century) and “*Khulāṣat al-ḥikmah*” (Summary of Wisdom) (Aghili, 2006) by Mohammad Husayn ibn Mohammad Hadi al-'Aqili al-'Alavi (from the 18<sup>th</sup> century) were checked in this review. The main source was Canon of Medicine and if there was a vague issue or for completion of a subject, the other sources in a hierarchy of older to newer were used and after deletion of repetitive issues, were added to this review. Furthermore, we reviewed databases such as IranMedex, PubMed, Google Scholar, Web of science, and SID (Scientific Information Database) using the keywords Anorexia, traditional medicine, and Persian medicine.

## Pathophysiology

Eating disorders are mental diseases with unknown causes. Twin studies showed that AN is not a purely acquired disease. Hereditary factors may also play a role in AN onset. Some genetic studies found a relation between several genes and

AN (Rask-Andersen et al., 2010). Investigations revealed that a combination of genetic susceptibility and environmental factors induce the disorder in young adults. There is an overlap between some genetic and environmental factors influencing AN and BN (Bulik et al., 2010). There is also some genetic overlapping between AN and obsessive-compulsive disorder (OCD) (Mas et al., 2013).

AN patients have visuospatial problems which may explain the body image disturbances observed in these patients (Favaro et al., 2012). They are metabolically normal at rest; But, when facing physiologic stressors, differ from the normal population (Heilbronn et al., 2007). The CNS, especially, the hypothalamus contributes to abnormal behaviour of eating in AN patients (Johansen et al., 2007). Neurobiology of eating disorders is attributed to the hypothalamus and brain stem (Zandian et al., 2007). Vulnerability of some AN patients to conflicts between punishment and reward suggests the involvement of some brain regions (anterior cingulate gyrus) may contribute to the pathophysiology of AN (Keating, 2010). Parietal cortex, anterior cingulate cortex and some parts of insula and temporal cortex probably contribute to body image perception (van Kuyck et al., 2009).

However, AN aetiology is unknown and seemingly, low food intake and increased physical activity might be considered as causes of initiation and aggravation of this disease. Low calorie dieting induces the release of corticotropin-releasing hormone (CRH) from the hypothalamus. Subsequently, dopamine will be released from mesolimbic dopamine neurons thus activating the locus coeruleus noradrenergic neurons in the brainstem. Both of these mechanisms are rewarding and AN patients enter an unwanted conditioning system. Neuropeptide Y is released following low food intake and starvation to maintain the body fuels for physical activity in order to provide a

condition for searching and preparing food (Sodersten et al., 2008).

Mood dysregulation, impulse control and appetite of AN patients are probably affected by brain 5-HT (serotonin) functions (Kaye, 2008). Some studies showed increased 5-HT<sub>1</sub> binding receptors in frontotemporal region and organic dysfunction of this area (Galusca et al., 2008). DA and 5-HT systems are disturbed in AN patient. Also, 5-HT might contribute to impulse control and altered satiety. DA may play a role in abnormal rewarding effects of meal (Kaye et al., 2013a). 5-HT attributes to satiety and serotonergic drugs can cause weight loss in humans by appetite suppression (Avena and Bocarsly, 2012).

The anorectic patients have increased physical activities following food intake (Zandian et al., 2007). These factors activate hypothalamic cells containing corticotrophin-releasing factor. These, in turn, activate mesolimbic dopamine neurons and noradrenergic cells of the locus coeruleus which push the AN patients to a cycle of reward and attention. This mechanism might explain the desire of patients to continue food intake avoidance (Zandian et al., 2007). Few studies showed increased responses of the caudate nucleus and posterior regions of insula in recovered AN. Attention to food stimuli has a negative impact on AN patients (Cowdrey et al., 2011). The AN patients showed decreased food-related somatosensory processing during satiety in Functional magnetic resonance imaging (fMRI) (Santel et al., 2006). The right lingual gyrus of AN patients showed diminished activation in time of hunger (Santel et al., 2006).

Adipocytokines including LEPTIN - a peptide secreted by adipose tissue - and adiponectin, neurotrophins, growth factors and peptides of GI systems have a role in appetite regulation. It is not clear that changes in circulatory adipocytokines and gut hormones in chronic AN patients are compensatory mechanisms or play role in

pathophysiology of the disease (Kowalska et al., 2011). Leptin suppresses appetite and ghrelin stimulates feeding (Chapman, 2004). Ghrelin induces the release of GH, and increases food intake and body weight. Ghrelin is an orexigenic peptide that activates the arcuate nucleus to release neuropeptide Y. (Keating, 2010) Neuropeptide Y that is synthesized in the brain, strongly stimulates food intake (Chapman, 2004).

Corticotropin releasing hormone, epinephrine/norepinephrine and dopamine systems may play a role in restlessness and desire for activity in AN patients (Casper, 2006). Alpha-MSH and CART (cocaine and amphetamine regulated transcript) are considered as anorexigenic peptides that will be released following activation of leptin receptors. Activation of leptin receptors suppresses the release of the orexigenic AGRP (agouti-related protein). It seems that a disturbance in opioid signalling that is attributed to feeding reward mechanisms of the brain, contributes to AN onset. Dopamine dysfunction is one of the possible reasons of anhedonia in AN patients (Rask-Andersen et al., 2010). Macrophage inhibitory cytokine-1, adipocytokine which was previously considered as a macrophage inhibitor, plays a role in satiety feeling in AN patients. High level of MIC-1 is seen in severely malnourished AN patients, like in cachectic patients that suffer from chronic diseases and cancers (Kowalska et al., 2011).

Avicenna and his followers believed that the causes of *botlan-e-shahvat* (anorexia) and *noghsan-e-shahvat* (dysorexia) are the same (Shah-Arzani, 2008). According to TPM, liver is one of the three main organs namely, the brain, heart and liver which have important roles in nutrition and growth. According to TPM concepts, the liver produces 4 humors (blood, phlegm, bile and black bile) as nutritional sources for other organs. Cardia, which is a highly innervated tissue also plays a role in feeling hunger.

Avicenna and other sages believed that in time of hunger, pancreas secretes *sodā* (black bile) on the cardia and it causes a burning sensation and subsequently, hunger. Disturbing each of these processes by internal or external disturbers leads to anorexia or dysorexia (Aghili, 2006; Shāh Arzānī).

Arzānī Muḥammad Akbar in *Mizan-al-Tib* remarked 7 causes for anorexia, as follow:

1. Simple warm or wet dystemperament in cardia.
2. Accumulation of morbid humors in the stomach.
3. Fullness of the body organs from crude phlegm which may lead to reduction of the organs' food demand.
4. Thickening of the skin and blockages of the pores which may lead to reduction of sweating and accumulation of morbid matters.
5. Liver failure and mesenteric vessel blockage.
6. Blockage of aperture between pancreas and cardia. Scholars of TPM believed that there is an aperture between cardia of stomach and *Tahāl* (the spleen and pancreas). There is no real aperture between the spleen and stomach; however, exocrine pancreatic hormones affect GI tract and contribute to digestion. It is close to function of *sodā*, secreted by *Tahāl*, which stimulates cardia of stomach as an orexigenic agent. In this regard, it seems that functions of *Tahāl*, in TPM, are divided into two parts: purification of blood which is conducted by the spleen and secretion of *sodā* which is performed by the pancreas.
7. Impairing the sensitivity of cardia to pouring of *the sodā* from the pancreas on the cardia. If the patient eats sour foods, he or she feels no increasing in his or her appetite; while in the blockages of the aperture between the cardia and pancreas, the appetite increases after eating sour foods

(Aghili, 2006; Nimrouzi et al., 2015; Shāh Arzānī).

### Clinical manifestation

AN patients show the personality traits and temperament that they had earned in childhood. These include obsessive behaviours, perfectionism, inflexibility, and harm avoidance as well as negative emotions. Some of these traits persist even after the patients gain normal weight following medical interventions (Kaye et al., 2013a). Serotonergic overactivity is attributed to some prominent features such as anxiety, increased satiety and obsessive compulsiveness, seen in AN patients (Connan et al., 2003). Anhedonia and asceticism in AN patients usually begin in childhood before the onset of eating disorders and persists even after the recovery from AN. Age-related hormonal changes in puberty, stress and societal pressure may exacerbate the symptoms in AN patients through inducing 5-HT dysregulation. Reducing the diet intake leads to diminished tryptophan serum level, the inducer of 5-HT dysregulation (Kaye, 2008). Women suffering from AN increase salivation, a higher autonomic response to food intake and disgust towards foods (Connan et al., 2003). In contrast to normal individuals, AN patients find eating stress-provoking and regard starvation as a way for stress relief (Kaye et al., 2013b). Many AN patients in advanced stage, experience an uncontrollable need for activity. It might be due to a need for thermal homeostasis and reaching the normal body heat level by increasing the activity (Hebebrand et al., 2003). However, symptoms of psychosis reported in some AN patients, may be related to the pathophysiology of the disease state rather than psychotic disorders (Miotto et al., 2010). Facing chronic overwhelming stress in adolescence periods may lead to submissive responses in AN females (Connan et al., 2003). Global meta-analyses showed that clinical symptoms

such as careful self-control in eating in AN individuals, correlate with brain structural changes (Titova et al., 2013). An abnormal response to oestrogen may contribute to some symptoms of AN in puberty period. This abnormal response to increased level of oestrogen in puberty period may be considered as an explanation for sex differences of AN (Young, 2010).

Regarding high levels of anxiety, AN patients suffer weaker emotional intelligence comparing to normal population (Hambrook et al., 2012). When food intake diminishes for long time, psychiatric symptoms increases. Impaired eating behaviour is attributed to psychiatric symptoms rather than BMI (Zandian et al., 2007).

### Paraclinics

Severely malnourished AN patients commonly show elevated transaminase serum levels (Hanachi et al., 2013). On the other hand, serum levels of brain-derived neurotrophic factor (BDNF) are significantly lower in AN patients as compared to normal adults (Rask-Andersen et al., 2010). Autoantibodies against melanocortin have been found in serum of AN and BN patients. It is suggested that these diseases may have an autoimmune origin (Johansen et al., 2007). AN patients' plasma leptin levels reflect their nutritional status (Kowalska et al., 2011).

Using brain imaging, it was shown that activities of some brain regions including frontal, cingulate, parietal and temporal cortices are altered in AN and BN. Diet restriction in AN may be a compensatory mechanism to reduce tryptophan availability and as a result, may decrease 5-HT disturbances to control the anxiety (Kaye et al., 2005).

Few studies showed lower acoustic startle response in AN patients, as compared to healthy individuals. ASR index shows the response of individuals to acute and sudden stimuli and comprises a sustained physiological pattern of muscle

contractions in arms and legs, blinking and changes of skin conductance and heart rate. These mechanisms help body protection and fight reaction in related conditions (Bellodi et al., 2013).

### Complications

Many organs may be affected by AN. Amenorrhea and osteoporosis are complications of AN. Oestrogen deficiency is a major cause of osteoporosis in AN (Legroux-Gerot et al., 2005). However, because of carbohydrate and protein variations in the diet and also shifting the oestrogen metabolism to low potency metabolites, patients do not respond to oestrogen supplementation. Even mild forms of AN may make the affected female patients vulnerable to increased fracture risk in their life (Bolton and Patel, 2001). The patients may develop electrolyte imbalance, acute kidney injury and ultimately kidney failure in the course of disease (Bouquegneau et al., 2012).

Recent studies failed to confirm the effectiveness of selective serotonin reuptake inhibitors – drugs using to increase brain 5-hydroxytryptamine activity - in treatment of AN patients denoting that alteration in serotonin neurotransmission may be attributed to the consequences of AN rather than being the causes of the disease (Zandian et al., 2007).

### Treatment

AN patients should eat the meals under a condition different from which anorexia had developed. External heat might accelerate the treatment. In an experimental study, external heat showed positive results in anorectic rats in a shorter course of treatment (Favaro et al., 2012). As most AN patients suffer from hypoestrogenemia and bone loss, oestrogen therapy may be beneficial (Ramos et al., 2012). Supervised exercise training may improve AN patients' cardiovascular status and strength (Ng et al., 2012). DHEA may induce weight gain

in some AN patients (Bloch et al., 2012). Brockmeyer et al. showed that in AN patients with lower body weight, lesser negative emotion retrieval would be experienced (Brockmeyer et al., 2013). Few studies have remarked that AN patients with better decision-making profile have better nutritional status after treatment (Cavedini et al., 2006). Women with AN and amenorrhea show acceptable responses to oestrogen therapy (Lebow and Sim, 2013). Supervised exercise training seems to be safe in AN and augment their strengths and cardiovascular status (Ng et al., 2013). Studies showed that meal supervision improves restoring weight of restrictive type AN patients (Kells et al., 2013). The chronic nature of AN leads to changes in the balance of body fluids and body spaces. Rapid treatment of AN patients may induce refeeding syndrome. Heart failure, rhabdomyolysis and Wernicke's encephalopathy are some manifestations of refeeding syndrome (Gentile et al., 2010).

Treatment should be performed gradually. Electrolytes (phosphorus and potassium) should be prescribed in first weeks of treatment in order to prevent electrolyte imbalances (Gentile et al., 2010). Leptin may prevent osteoporosis in patients with chronic AN. Ghrelin with orexigenic effects can facilitate nutritional restoration (Stoving et al., 2009). Fluoxetine may be useful in the prevention of relapse in AN patients (Kaye et al., 2001). There is no evidence that psychoactive drugs have positive effects on AN patients (Södersten et al., 2003). Due to sympathetic activity, AN patients, in course of treatment and refeeding stages, may report heart rate elevation and palpitation (Yoshida et al., 2006).

According to TPM viewpoint, in anorexia with simple dystemperament, the physician should attempt to balance the temperament (*mezaj*) with foods and medicaments of opposite quality of that of the temperament. In case of accumulations of morbid matters in stomach, compounds

like honey and vinegar mixed with radish and mustard seeds, should be prescribed. In liver malfunction, freshener and astringent foods with warm *mezaj* like cinnamon, saffron and pomegranate seeds are recommended. In case of cardia's weakness, the brain tonics like chickens and cooked peas flavoured with saffron and rose water are recommended (Aghili, 2006).

According to traditional views, habits (lifestyle), mental conditions such as depression and grief, spiritual diseases (neuro – psychological) and gastrointestinal worms are the other causes of reducing appetite. For elimination of worms, *sekanjabin-e-safarjali* (an oxymel containing Quince juice), lemon juice, onion in vinegar pickle, peppermint distillate, salted fish in vinegar, sour pomegranate and pennyroyal drink are recommended (Aghili, 2006). Herbs of warm temperament may increase appetite in anorexic patients with cold temperament. AN patients usually receive low intake so they are thin and weak. Based on TPM, medicines and foods of warm temperaments (such as pea soup and mustard) could be useful for those patients (who has cold temperament) (Nimrouzi and Zarshenas, 2015b). Other recommended herbs known as appetite stimulant in TPM are common fumitory, chick pea, celery, anise, feverfew, ajwain, crataegus, radish, oregano, leek, mastic, and yellow nutsedge (EMARATKAR et al., 2012).

### Prognosis

The outcome of AN management is poor (Sodersten et al., 2008). Brain neurodevelopment impairment and abnormalities in the hypothalamic–pituitary–adrenal (HPA) axis in adolescent girls with AN may persist even after restoring their weight (Connan et al., 2003). These patients show no significant behavioral changes even following successful treatment, and achieving normal weight and physiological functions

(Heaner and Walsh, 2013). Vomiting is a negative prognostic factor in people recently recovered from AN (Zerwas et al., 2013). Hyperaminotransferasemia reflects a poor prognosis in severely malnourished AN patients (Hanachi et al., 2013). High levels of ghrelin and growth hormone (GH) are observed in severely emaciated AN patients. Eating behavior and nutritional status in these patients are related to GH and ghrelin levels (Tanaka et al., 2004). Shibuya et al. reported that salivary cortisol may be used as a biomarker to assess the severity of AN in children (Shibuya et al., 2011). Physical exam of AN patients usually shows bradycardic, hypothermic and dry and yellow skin signs. Leptin levels are at the lowest level in AN patients. Amenorrhea and osteopenia are common complication of chronic AN (Mitan, 2004).

### Discussion

Currently, it is believed that satiety is controlled by a wide integrated network of a brain parts (Rolls et al., 2010). A barrier in AN patients' treatment is hyperactivity of patients. Following food shortage and starvation, the temperature becomes lower, fat storage decreases, heart rate reduces and serum level of leptin are decreased. The behavioural responses are more complicated and less understood in food storage. An important compensatory behavioural response is increasing the capacity for activity. In predator animals, this response may be a survival mechanism to seek for foods and hunt. In time of famine, this mechanism is also seen in humans. In contrast, in times of plenty, easy access to food and increased food intake lead to inactivity. This is a familiar cause of high prevalence of obesity in some developed countries (Scheurink et al., 2010).

Hyperactivity in AN patients is a rewarding phenomenon. Through time, it becomes an addiction behaviour due to release of endogenous opioids. In body

dysmorphic disorders, patients have unhealthy over-attention towards the details of specific parts of their bodies (Madsen et al., 2013). Orexigenic neurons in lateral hypothalamus and dopaminergic neurons of the mesolimbic system probably play important roles in rewarding mechanisms underlying AN pathophysiology. Dopamine depletion, dopamine blockade and use of selective orexin 1 receptor antagonist may control the hyperactivity in starved rats (Scheurink et al., 2010).

Ghrelin is an endogenous ligand for growth hormone secretagogue (GHS) receptor in gastric mucosa. GH inhibits glucose oxidation and glycogen synthesis in muscles and subsequently, decreases glucose utilization in periphery and increases hepatic glucose output. GH also exacerbates insulin resistance by increasing the levels of free fatty acids in circulation. In prolonged fasting, counter regulatory hormones such as GH, catecholamines, cortisol and glucagon antagonise the insulin effect and thus, prevent further reduction in glucose blood level. These factors provide energy required for activity during physical exercise. Intake of high protein foods increase the GH level. Circulating levels of leptin has a positive correlation with the amount of lipid stores and body fat mass. In overt obesity with high circulating leptin levels, GH secretion is highly suppressed. Ghrelin reduces fat oxidation, but stimulates GH secretion and food intake. Increasing levels of ghrelin in fasting periods increase meal intake through stimulating the GH secretion and possibly inhibiting insulin secretion. Contrary to obese patients who represent hypersensitivity to GH, AN patients show GH resistance (Scacchi et al., 2003). Studies showed that AN patients are probably protected from drug abuse (Kaye et al., 2013b). AN may protect the patient from becoming overweight later in life. The lifetime prevalence of AN is about 1.20% in females and 0.29% in males



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(Bulik et al., 2006). On the other hand, binge eating behaviour in binge-eating type of anorexia nervosa (BN) is probably attributed to increased level of ghrelin (Stoving et al., 2009).

*Zingiber officinale* Roscoe, a potent stimulator of pancreatic amylase and intestinal lipase activity, decreases intestinal transit time in rats and increases the appetite in shrimp in post larvae stage of life (Venkatramalingam et al., 2007).

Vinegar is known as a natural appetizer and using vinegar as a supplement increases subjective report of satiety through diminishing postprandial responses of insulin and blood glucose (Östman et al., 2005), although a recent study suggested that satiety suppression by vinegar is more related to its poor tolerability for GI tract and inducing nausea rather than orosensory stimulation and being a natural appetizer (Darzi et al., 2014).

According to TPM sources, vinegar and oxymol in limited amounts, are appetizer but if taken after meal and especially in excessive amounts, spoil digestion and may induce GI symptoms like nausea in some cases. In this regard, inducing nausea and increasing feeling of satiety are in line with findings of recent studies (Darzi et al., 2014), but in the case of stimulating appetite, it should be noticed that the recommended dosage and time of consumption of vinegar and oxymol are different from those advised by conventional modalities as appetite blockers. In TPM, drinking oxymel is suggested before meal to quench dominance of bile and induce appetite by stimulation of cardia and cleaning the surface of stomach from phlegm (Aghili, 2006). Markey et al. found no appetizing effect for a 3-gram single dose of cinnamon and gastric emptying after taking a high fat meal (Markey et al., 2011), however, TPM recommends to use appetizers before meal. Appetite stimulant activity of cinnamon, based on animal

studies, is probably because of Ammameldehyde (Tipu et al., 2006).

Although the pathophysiology of AN in TPM is different from ???, TPM criteria for treatment of anorexia is similar to those of conventional views. Despite complex hormonal explanation, the etiology of AN in conventional approach is not completely understood. In TPM approach, the etiology and recommended interventions are thoroughly defined based on humoral pathophysiology. Recommending to have spiritual support and a healthy lifestyle are common in both views. Temperament and predominance of humor are two main factors for designing an intervention and treatment plan in TPM.

Apart from differences in views of conventional and TPM approach, medicinal herbs recommended in TPM are worth to be examined by precise clinical trials.

#### Conflict of interest

Authors of this manuscript have no conflicts of interest.

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