

## Role of Heart and its Diseases in the Etiology of Depression According to Avicenna's Point of View and its Comparison with Views of Classic Medicine

Mohammad Yousofpour, Mohammad Kamalinejad<sup>1</sup>, Mohammad Mahdi Esfahani<sup>2</sup>, Jamal Shams<sup>3</sup>, Hassan Hoshdar Tehrani<sup>1</sup>, Mohsen Bahrami<sup>4</sup>

Department of Traditional Iranian Medicine, Traditional and Complementary Medicine Research Center, Mazandaran University of Medical Sciences, Sari, Iran, <sup>1</sup>Department of Pharmacognosy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran, <sup>2</sup>Department of Iranian Traditional Medicine, School of Iranian Traditional Medicine, Research Center of Quran, Hadith and Medicine, Tehran, Iran, University of Medical Sciences, Tehran, Iran, <sup>3</sup>Department of Psychiatry, Behavioral Science Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, <sup>4</sup>Department of Iranian Traditional Medicine, School of Iranian Traditional Medicine, Tehran University of Medical Sciences, Tehran, Iran

### Correspondence to:

Dr. Mohammad Kamalinejad, Department of Pharmacognosy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Vali-e-Asr Avenue, Niayesh Junction, P.O. Box: 14155-6153, Tehran, Iran. E-mail: mkamalinejad@yahoo.com

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### ABSTRACT

**Background:** Depression is one of the most important medical problems in today's world; despite its high prevalence, its causes unfortunately remain not fully known. Among important issues regarding this is its relation with heart diseases. Based on studies this comorbidity increase morbidity and mortality and leads to worst prognosis. However the cause of such high rate of comorbidity is unclear and instead of efforts to understand this correlation has prompted the medical world to consult other medicinal disciplines, not only to find the answer but also to increase the effectiveness of treatment and decrease its cost.

**Methods:** We first reviewed the most important ancient causes for depression mentioned by Avicenna and considered those as the key words for our next step. Then, we made a literature search (PubMed and Scopus) with those key words to find out new scientific findings in modern medicine about the Avicenna's suggestions.

**Results:** Avicenna does not regard depression as only a mental ailment, but as a disorder resulted by the involvement of brain, heart and blood. He believed that the main causes of depressive events are rooted in heart diseases; in most cases brain is only affected secondary to the heart. Thus he declared that for the treatment of depressive disorders, the underlying cardiovascular diseases should be considered.

**Conclusions:** It is worthwhile to consider the Avicenna's recommended causes of depression and to design future scientific studies based on his suggestions.

**Keywords:** Avicenna, cardiovascular diseases, depression, heart diseases, treatment

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## INTRODUCTION

Many studies over past 2 decades show depression disorder is one of the most important world health problems. According to the WHO reports, depression will be the second cause of disability, after heart diseases, in the developed countries toward 2020.<sup>[1]</sup> World Health Survey also showed that depression is more harmful on

man health than other diseases such as angina, arthritis, asthma and diabetes.<sup>[2]</sup>

Unfortunately despite the high prevalence of depression, it is difficult to manage the disorder because its causes are largely unknown.<sup>[3]</sup> The other important subject which many researches engaged in is how to find correlation between depression and cardiovascular diseases (CVDs).<sup>[4-9]</sup> Various studies have reported a noticeable range of 14–50% of heart diseases comorbid with depression.<sup>[10-13]</sup>

Heart disease along with depression have produced bad prognosis in rate of relapsing and high rate of mortality because of heart illness.<sup>[4,5,8,14-19]</sup>

Therefore, it is necessary to clear up the obscure points connected with the disorder in order to control and prevent the deleterious effects of depression. The use of conventional medicine strategies in combination with traditional ones can be an important way to increase our capacity to recognize and treat disease as well as reduce side effects and costs.<sup>[20,21]</sup>

One of the oldest and gorgeous school of medicine in the world is the Persian Medicine (PM)<sup>[22]</sup> which has introduced some nominated scientist such as Mohammad Ibn Zakaria Razi (Rhazes) and Ibn Sina (Avicenna). Avicenna is a famous Persian philosopher, thinker, and physician whose medical book named The Canon of Medicine has been taught in the European Universities of Medical Sciences such as French Monopoliea and Belgian Louvain university for many centuries.<sup>[23-25]</sup>

In the Canon of Medicine, Avicenna describes various kinds of *Mālikhūliyā* (melancholia) disorders as the subtitle of brain disorders. One kinds of melancholia is called cerebral melancholia with symptoms very similar to depression in the today's psychiatry [Table 1].

Based on Avicenna, etiology of cerebral melancholia originates from heart diseases characteristically this kind of melancholia. None of the physicians before Avicenna, like Rufus, Hippocrates, Galen, Muhammad ibn Zakariyya al-Razi (Rhazes), Zahravi, have not mentioned any heart involvement in the melancholia etiology, although some scientists such as Rhazes have made some advice to increase heart power in the process of melancholia treatment. Therefore, in medicine history, Avicenna is the first one who propounded correlation between cardiac disease and melancholia.<sup>[26]</sup>

At the present, studies have shown the above coexistence, and they discuss that depression is an important independent risk factor in CVD.<sup>[27,28]</sup> However, Avicenna believes that in most cases, some

**Table 1: Comparison of symptoms of melancholia in PM with major depression on the basis of DSM-IV-TR diagnostic criteria**

Melancholia (PM)	DSM-IV-TR criteria for major depressive
Excessive sorrow for no reason and crying	Depressed mood
Despair, affinity towards seclusion, isolation	Markedly diminished interest or pleasure in all or almost all activities
Emaciation	Significant (> 5% body weight) weight loss or gain
Excessive appetite	Increase or decrease in appetite
Insomnia, hypersomnia in individuals of phlegmatic temperament ament	Insomnia or hypersomnia
Agitation and restlessness	Psychomotor agitation or retardation
Dullness, decrease in physical motility	Fatigue or loss of energy
Excessive morbid fantasies	Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional)
Excessive thought, perpetual obsession	Diminished ability to think or concentrate
Preoccupation with death	Recurrent thoughts of death (not just fear of dying) recurrent suicidal ideation

PM=Persian Medicine, DSM-IV-TR=Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> Edition, Text Revision

heart diseases start a process which ultimately results in depression and if the cause of depression in some cases originates from the brain, heart diseases make the problem worse. Therefore, according the Avicenna's view, heart illness plays the main etiologic role in the most cases and in few events, shows a magnifying role on the depression.<sup>[26]</sup>

In spite of many studies on the depression and its approved complicated correlation with some heart diseases in the 2 past decades.<sup>[27]</sup> There are still many questions on how the etiology and treatment of depression are specially when it coincident with heart disease. For instance, however, depression in heart patients, increase the chance offside effects, recurrence of cardiac events, and its mortality rate<sup>[15,27,29,30]</sup> but unfortunately clinical trial studies have not so far shown that medical treatment of depression or psychotherapy can reduce significantly side effects or recurrency or the mortality of heart diseases.<sup>[27,31,32]</sup>

In the present study we describe Avicenna's view on the depression etiology, showing some new finding confirming his view, and discuss possible mechanisms of how some heart diseases might be the main reasons of depression on the basis of PM, hope to open new approach for researchers on the etiology and treatment of depression.

## METHODS

The most reliable references on Iranian ancient medicine were determined on the basis of the following criteria:

- Being the most used books by ancient physicians
- Author's credibility
- Being the most cited references in papers published in peer-reviewed national and international journals in recent years.

Once reliable references were determined, literature search was initiated to collect data in accordance to the following steps: *Mālānkhūlīyā*, *VasvaseMālīkhūlīyāiee* (melancholic obsession), and *Mālīkhūlīyā* were picked as keywords:

- All data relevant to the treatment of melancholia was collected
- All nonpharmacological interventions of melancholia were extracted
- Common points in various references about etiology of cerebral melancholia (depression).

Furthermore, the following keywords were used to search the PubMed and Scopus databases: Melancholia, depression, traditional medicine, CVDs, myocardial Infarction (MI), and cardiac arrhythmias.

## RESULTS

### Heart physiology by the persian medicine approach

Heart is the first organ which starts motion when the fetus gets life, and it is the last part to stop motion when death occurs.<sup>[33]</sup> Before discussion on heart physiology, it is necessary to describe briefly some fundamental subjects of the PM school. One of these subjects is the Humors.

Humors are wet and fluid matter which are produced by the liver and transferred to the heart by inferior vena cava vein and then to the other parts of body by aorta artery in order to replace the substance used by metabolism. Humors include blood, phlegm, yellow bile and black bile (atrabile). Each of these quaternary humors have a pair of different qualities of hot, cold, wet and dry forms that is, blood is hot and wet, phlegm is cold and wet, yellow bile is hot and dry and black bile is cold and dry.<sup>[26]</sup>

Another important subject in the PM is "Mezaj" (temperament). Temperament is resulted by interaction of two opposite qualities of humors which ultimately give rise to a homogenous quality named "Mezaj" (temperament). To explain more, suppose that when sugar dissolves in water, produces a solution which is fluid (as water) and sweet (as sugar). This solution gives a homogenous quality which is called "Mezaj."

All the organs of body have their specific temperaments. For example, brain has a cold and wet temperament, heart

a hot and dry and liver a hot and wet temperament. The combination and interaction of all organ temperaments leads to man's special temperament. As long as this special temperament remains intact, man lives in healthy condition. But when his temperament homeostasis changes, a process arises which ultimately causes leads to illness, a condition may be called dystemperament.<sup>[26,34]</sup>

Avicenna scientists believe that humors are divided to thin and thick substances based on their viscosity. Thick substance plays role on the formation, growth, feeding and stability of body organs. But thin humors, or so called humors vapor, when settled down in the left ventricle of heart converts to a "spirit" through a complicated procedure by which all the body organs are given vital, so, this spirit is called vital spirit or cardiac spirit. The existence of vital spirit in man's body means that he is alive, and lack of vital spirit means man death.<sup>[26]</sup> From the point of physician's view the spirit is not, of course, anon material object such as considered in philosophy science, but has a material identity and contains very thin compounds like air, so that it has been referred to as a vaporous spirit as well.

On the basis of PM, being produced by left ventricle, vital spirit spreads out all over the organ through aorta artery, so gives them life.<sup>[35]</sup> When vital spirit travels from heart to brain base via two carotid arteries, its temperament, in a network formed in this region by these and other artery branches (Willis net) will change and convert to sensual spirit which transfers sense and motion to all body organs including heart through nerves. When vital spirit reaches liver, the same changes occur and vital spirit converts to "natural spirit" with its duty is promotion of body growth and feeding.<sup>[35]</sup>

Therefore vital spirit in heart correlates with sensual spirit in brain and natural spirit in liver, and all of them have cross interactive effect with one another. Avicenna scientists believe that each of these triple spirits carries one faculty or talent and does its own tasks through these triple faculties, including vital faculty, sensual faculty, and natural faculty.

On the basis of PM, similar to vital spirit, vital faculty is originated from heart. This faculty is divided in two parts, one is active, and the other is passive power. The duty of active power is cardiovascular constriction and relaxation, and passive power export source emotional states such as happiness, sorrow, anger, fearfulness, braveness, enjoy, etc.<sup>[26,35]</sup> The reason why these emotions are linked with heart, is that these emotions were shown to cause the contraction and relaxation of heart spirit, and it in turn causes heart contraction and relaxation.

Avicenna and other physicians have demonstrated the effects of emotion on the cardiovascular system by pulse

**Table 2: Pulse changes in emotional conditions**

Emotion	Pulse alterations
Anger	Large, high, swift, frequent
Sorrow	Weak, small, different, tardy
Sudden fear	Swift, tremulous, varied, irregular
Joy, pleasure	Large, different, tardy, soft

variations which again prove the correlation of these emotions with heart<sup>[26,34]</sup> [Table 2].

Conventional medicine, although assumes that emotional behaviors are controlled by brain and limbic system, but researchers confirm that there is a correlation between negative and positive emotional states, like, happiness, despair, sorrow, fear, and health specially cardiovascular health.

The last important point in this section is that heart and brain have bilateral and direct connection each other. The most important connection of heart to brain is made by vital spirit towards sensual spirit through arteries, and the most important connection of brain with heart is also through sensual to vital spirit mediated by nerves, and so these two important organs, have directly reciprocal effects on each other.

### Melancholia (description, variety)

Melancholia has been classified as one of the mental illness in PM and is described as an illness produced by changes in the quality of brain temperament (mental state) and prevent man from right thinking and common sense so that in patient falls is sorrow mind, fear and suspicion without any apparent reason.<sup>[26,34,36]</sup>

It is named because it was believed that the main cause of this illness comes from abnormal increase in black bile.<sup>[34]</sup>

Melancholia is divided into three classes according to which organ the black bile has been accumulated in:

- If black bile is concentrated in brain, it is called cerebral melancholia
- If black bile is condensate in organs such as stomach, liver, bladder, and extra peritoneal, it is named peritoneal melancholia (mālenkholia-l-marāqqī)
- If black bile spreads all over the body, it is called systemic melancholia.

### Depression and melancholia

In Table 1, melancholia symptoms in PM are compared with major depression on the basis of Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> Edition, Text Revision (DSM-IV-TR) diagnostic criteria.<sup>[26,37]</sup> In addition to this table, in DSM-IV-TR, in the subgroup of mood disorders along with description of various depression disorders, melancholic disorder is also mentioned and its diagnostic criteria are described. Thus, melancholic disorder has been classified as one of the depression disorders in this accredited classification system.<sup>[37]</sup>

### Avicenna's view in etiology of melancholia

Avicenna in describing the role of blood in producing brain diseases like melancholia, discusses that if the blood in transferring from heart to brain is bright, dilute, clear and enlivening, in other words, its physicochemical properties are natural, not only plays a major role in brain healthy, but also makes it resistant against illness, and even if mental illness is in initial stages, most probably prevents its outbreak, but if physicochemical properties of blood in going from heart to brain change, as in cardiac black bile disease, cause brain corruption and produce diseases such as melancholia.<sup>[26]</sup>

According to Avicenna's view, blood variations followed by cardiac illnesses are in most cases initiators of melancholia, although its solidity is formed in brain. Avicenna, of course, states that there may be other reasons apart from heart illness which causes melancholia, but, he insists on, they cannot cause this mental illness without heart collaboration. Therefore, from the point of Avicenna's view the most important and greatest reason of melancholia illness roots in black bile-affected cardiac diseases.<sup>[26]</sup>

## DISCUSSION

### Avicenna's view and new studies

At first, it should be mentioned that with common signs of mental melancholia as it referred to in PM, and depression in conventional medicine [Table 2], these two illnesses have a common root, and so, some important points about melancholia made by PM physicians such as etiology and treatment can be applied usefully to depression.

The relation between some heart diseases and depression has been revealed in the last 2 decades<sup>[38-41]</sup> is the same as those mentioned clearly by Avicenna in his Canon book a 1000 years ago. There is, however, a difference in expressing this kind of relation. Avicenna explains it clearly on the basis of PM, but today researchers describe it as a two comorbid condition and only give some probable mechanism for it.<sup>[27]</sup>

The high incidence of depression, approximately 14–50% among various heart diseases shows that these two illnesses come together in the most of the time.<sup>[10-13,42]</sup>

As a result, the American Association of Cardiovascular and Pulmonary Rehabilitation strongly recommended that patients with heart disease should be screen for depression and refer for cardiac rehabilitation protocols containing food, stress management, and exercise.<sup>[27]</sup> Blumenthal *et al.* in their studies of Standard Medical Intervention and Longtime Exercise (SMILE) found that exercise is more effective than medical treatment on the reduction of depression.<sup>[43]</sup>

In addition, considerable increase of depression disorders in cardiac patients compared to common healthy population on one hand,<sup>[6,39]</sup> and recurrent depression increase following heart disease on other hand<sup>[44,45]</sup> raises up a viewpoint that some heart diseases may bring conditions which ultimately result in depression. This is what has been referred to by Almeida *et al.*<sup>[3]</sup>

However, an important question arises which makes the relation between these two diseases more complicated. The question is why, in clinical trials studies, treatment of depression in patients with heart disease have not decreased recurrent heart disease incidence or mortality considerably and has been just effective on patient acceptance of drug treatment protocol, and his life quality,<sup>[27]</sup> in spite of studies demonstrating that depression increases the occurrence of new heart diseases,<sup>[4]</sup> morbidity and mortality,<sup>[15-18,28,46]</sup> and MI,<sup>[30]</sup> several times in cardiac patients? In other words, if depression disorder is the only reason for four times increase in MI<sup>[9]</sup> and 2.7–5 times increase in cardiac patients mortality,<sup>[27,19]</sup> why has treatment of depression not considerably decreased MI or cardiac mortality!?

The pessimistic results of the above studies as well as the lack of randomized placebo-controlled studies in demonstrating that the depression treatment has useful clinical effect on CVD,<sup>[31,32]</sup> raise serious doubt on whether depression disorder may give rise to a bad prognosis in depressed cardiac patients. That is why some scientists make suggestion that depression itself is not probably the main cause of bad prognosis in depressed cardiac patients.<sup>[40,47]</sup>

It seems possible to find answer from Avicenna's view for the above question, as he clearly speaks out about the etiologic role of some heart diseases on depression outbreak, and believes that these diseases make the most important cause of depression disorder. He, then, describes the role of physicochemical changes of blood properties on producing depression. This means he does not think that depression is just brain disease, but it is believed that depression is a multi-system disease, in addition to the brain, cardiovascular system and blood circulation is impaired. He, therefore, emphasizes that for depression treatment there is no way but by treating disorders of these systems along with mental therapy.<sup>[26]</sup>

At present, it is shown that cardiac arrhythmias<sup>[48]</sup> increase of blood pressure secondary to high levels of cortisol<sup>[49]</sup> and decrease of heart rate variability,<sup>[50-52]</sup> increase of plasma level of platelet factor IV and beta-thromboglobulin, which cause raising platelet activity, endothelial vascular damage,<sup>[53,54]</sup> and thrombosis, and high levels of cytokines such as interleukin 1, interleukin 6, Tumor Necrosis Factor (TNF), which play key roles on atherosclerosis,<sup>[55-57]</sup> have been documented in depressive patients.

In overall, it must be said that all the above conditions are in accordance with Avicenna's views of multi system causes of depression.

In addition some researchers confirm the effect of collective of various biological systems on depression disorder. Among them is Dr. Peter Kramer, who writes in his book under the title of "Against depression."

"Depression is not a brain disease merely; it is also a neurological, hematological, and CVD."<sup>[58]</sup>

Thus it seems that depression is not just cerebrally originated, because with such a vision, it should not result in bad prognosis for cardiac depressive patients. The failure of depression treatment on reducing morbidity and mortality should be rooted in multiple organs of depression disorder.

It is believed that in conventional medicine, limbic system, especially its area of reward and punishment centers, control of excitement, but scientists have confirmed there is a link between positive and negative emotions, such as sorrow, anger, happiness, and health specially cardiovascular health.

That is, positive emotional states like optimism, hope, delightfulness, reduce CVD and increase life long time, but negative emotions like hostility, fear, sever and continuous anger cause cardiovascular problems and life time shortage.<sup>[59,60]</sup> Some studies by Kapfhammer have shown that some depressive symptoms such as anhedonia, hopelessness, and vital exhaustion, have close connection with CVDs, and so proposed that these symptoms mediate, as a specific risk factor, correlation between heart disease and depression.<sup>[39]</sup>

There is an important point in PM, that is although emotion states are correlated with vital faculty and spirit, but these states, as the scientists believe, are under control of cardiac and blood temperament. To explain more, if a person has a heart with hot temperament, and his blood is dilute and clear and its quality is hot, he is, therefore, a hopeful man with happiness tendency, because of his dilute and clear blood but he tends to be anger, because of his hot heart and blood temperaments, although his angriness rises sharply then disappears quickly because of his dilute blood.

Now, consider another person; he is with hot heart and blood natural temperament, but his blood is thick and turbid (not clear and dilute). Here, the man is in sorrow (because of blood turbidness) and anger (because of hot heart and blood temperament) tendencies, but his angriness is stable and does not diminish quickly (because of condensed blood). There is a third person who, opposite to the two above persons, is with cold heart and blood natural temperament, and his blood is thick and turbid (like the second person). This man is



coward and slow-witted (because of cold heart and blood temperament) and has a sorrow tendency (as his blood is turbid) and his emotional states disappear slowly (since the blood is thick).

Today, some scientists<sup>[27]</sup> believe that it is possible to present more precise view on the origin of depression and its correlation with heart diseases if more knowledge is collected for the following questions:

- Why do some patients with heart diseases show the best response to the treatment but some others do not?
- Why do some patients fall in depression quickly after a heart accident, but some others show delayed or no depression?
- Which group of depressive patients with heart diseases will demonstrate good prognosis, and which one will give bad prognosis?

We believe that if future studies focus on cognition exact of blood-cardiac temperament, it will be possible to find acceptable answers to the above questions.

Today, the most probable mechanisms of relation between depression and CVD are proposed to be the change of bio-behavioral routes. From these routes, the changes of inflammatory and immune responses are considered to be important as this ends in bad prognosis. In addition, there is another hypothesis that structural and functional changes of left ventricle can also precede clinical symptoms appearing in depressive patients.<sup>[40]</sup> Some other studies have also shown that functional disorder of left ventricle is in connection with rising higher risk of depression after MI.<sup>[61,62]</sup>

The functional disorder and structural changes of left ventricle in depressive patients is in accordance with the view of Ibn-e-Sina and other scientists of PM in that the mechanism of how cardiac disease is related to depression is the connection of vital spirit produced in left ventricle with brain sensual spirit.

## CONCLUSIONS

Based on Avicenna, depression is not only a cerebral disease, but also is a multi-system disease; in addition to the brain, cardiovascular system and blood circulation are involved. Avicenna believes that in most cases, some heart diseases initiate a process which ultimately leads to depression and if the cause of depression in some cases originates from the brain, heart will be involved and make the problem worse. Therefore, according to Avicenna's view, heart disease and blood changes, in most cases have important role in etiology of depression, play as initiator and in a little cases, behave as aggravator factors. Therefore, He, emphasizes that depression don't be treated without treatment of heart disease.

Considering high prevalence of depression among patients with heart disease, which is shown in recent studies, we think that Avicenna opinion may be correct too relates of heart disease and depression. We suggest neuroscientists study this relation on available animal models of depression, such studies we can't found in our searches.

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