Review Article

Trends in Pharmaceutical Sciences and Technologies 2025: 11(4):309-320.

A Comparative Analysis of Black Bile in Ancient Medicine and Oxidative Stress in Modern Science: Insights into Chronic Disease and Dietary Interventions

Majid Nimrouzi[1,2];Ph.D, Abdolali Mohagheghzadeh[3];Ph.D, Ghazaleh Mosleh[3*];Ph.D

[1]Research Center for Traditional Medicine and History of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Department of Persian Medicine, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Department of Phytopharmaceuticals (Traditional Pharmacy), School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran

Abstract

Black bile (Sauda) as one of the four humors from Persian medicine has links with melancholic temperament, gut issues, aging process, and also some cancer-related conditions. Some recent studies have discovered similarities between the systemic implications of black bile and oxidative stress which highlight how internal imbalances can mess with our body systems, leading to various dysfunctions. A systematic review of traditional and modern references was conducted on the role of black bile in ancient medicine and its comparison to modern oxidative stress. The authors analyzed articles from databases including PubMed, Scopus, and Google Scholar and Traditional Persian Medicine (TPM) texts. According to traditional medicine, restrictions of melancholic foods such as lentils and salty meats while intake of warm, moist foods like soups and herbs (ex. basil and mint) could treat excess black bile. The traditional approaches and new antioxidant diets stress the importance of individualized life and dietary interventions to remove oxidative stress. It targets the herbal capacities to neutralize reactive oxygen species (ROS) and the harmful impacts of chronic inflammation and mood disorders caused by an internal imbalance. The analogy between oxidative stress and black bile suggests that the integration of ancient wisdom in medical practice and antioxidant therapy could lead to innovative solutions in the management of intractable diseases such as cancer, irritable bowel syndrome, and other chronic diseases. Future investigations should explore the potential of blending traditional humoral therapy and biomedical therapy in an effort to develop more comprehensive regimens for multi-morbidity diseases.

Keywords: Medicine; Depressive Disorder; Reactive Oxygen Species; Gastrointestinal Disorders; Cancer

Please cite this article as: Nimrouzi M, Mohagheghzadeh A, Mosleh G. A comparative analysis of black bile in ancient medicine and oxidative stress in modern science: Insights into chronic disease and dietary interventions. Trends in Pharmaceutical Sciences and Technologies. 2025;11(4):309-20. doi: 10.30476/tips.2025.106812.1296

1. Introduction

Ancient Greek and Persian medicine relied on the theory of the four humors, first described by Hippocrates. Under this framework, the health of the body turns on a balance of four bodily "humors" called blood, black bile, yellow bile, and phlegm. Each humor is attributed to certain qualities, temperaments, and physical characteristics. Black bile, or Sauda in Persian, is related to cold and dry attributes. Black bile, normally formed through the burning of other humors, has been associated with melancholic disorders. A prolifera-

Corresponding Author: Ghazaleh Mosleh, Department of Phytopharmaceuticals (Traditional Pharmacy), School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran
E-mail: Moslehgh@sums.ac.ir

Received: 16/04/2025; Accepted: 01/09/2025

tion of black bile is thought to upset the body's homeostatic juggle, resulting in things like depression, digestive ruckus, or cancers (1). The effects it has on the mind and body indicate that too much black bile could upset the metabolic workings (2, 3).

With the advent of modern biomedical science, the rise of empirical science (18th and 19th centuries) eventually brought about the decline of humoral theory. Western medicine has gradually shifted from traditional theories through a move toward anatomy-oriented and cellular pathological concepts (4, 5). In biomedicine, oxidative stress is identified to be the imbalance of the reactive oxygen species (ROS) production and the ability of organisms to counteract the detrimental effects of ROS through neutralization by antioxidants. ROS are the byproducts of cell metabolism. Yet they build up too much and cause damage and inflammation within cells, and they also are responsible, in part, for chronic disorders, including depression, gastrointestinal disorders, and various forms of cardiovascular disease (6, 7).

ROS are important for the maintenance of tissue homeostasis. They govern signaling and differentiation processes but may also cause cellular injury and death (8). This biological model is increasingly being recognized as pertinent to the development of chronic diseases. The damages caused by ROSs on DNA, proteins, and other cellular components, including lipids, activate the inflammatory pathways that lead to the progression of several ailments, e.g., neuro-inflammation in depression and inflammation of the gut in gastrointestinal disorders (7, 9). Additionally, tumor cells are enriched with ROS. It is known that some of the ROS-related genes can interact with DNA repair genes, keep ROS in balance, and promote cancer cell proliferation (10, 11).

In contemporary cancer research, oxidative stress---an imbalance between ROS formation and antioxidant defenses---is known to be an important mechanism involving the initiation, progression, and metastasis of tumors. ROS can lead to DNA damage and subsequent mutations, (as well as Delet) and also activate inflammatory-mediated signaling pathways, both of which are implicated in carcinogenesis. Rationally, ROS triggers pathways, including PI3K/Akt/mTOR and MAPK, which are important in tumor growth and angiogenesis (10, 12).

These emerging insights into the systemic role of oxidative stress provide a compelling modern parallel to the ancient concept of black bile. Both frameworks conceptualize a pervasive, systemic imbalance that acts as a pathophysiological cornerstone for chronic disease. In both models, this imbalance originates from internal processes—described in ancient terms as the "combustion" of other humors and in modern terms as the metabolic production of ROS. When these entities accumulate beyond the body's capacity to manage them, they are understood to disrupt the function of multiple organ systems. This disruption manifests clinically in strikingly similar patterns, including mood disorders like depression and melancholia, gastrointestinal ailments, and a predisposition to conditions like cancer. Consequently, the therapeutic strategies in both systems converge remarkably. The ancient prescription of "warm and moist" foods and herbs to counteract the "cold and dry" nature of black bile finds its modern correlate in dietary regimens rich in antioxidants and anti-inflammatory compounds, which are designed to neutralize ROS and mitigate inflammation. This parallel suggests that these historically distinct medical paradigms are identifying a similar core phenomenon of systemic dysregulation and addressing it through conceptually analogous, system-balancing interventions (13, 14).

Black bile has been largely discarded by modern medicine. Yet within the construct of oxidative stress, black bile holds incredible potential insights. In both systems, the importance of balancing internal factors to moderate them with external ones through dietary and lifestyle interventions is emphasized, whether through balancing the four humors or mitigating oxidative damage. This review discusses and provides detailed links that traditional medicine wisdom may have something to offer in order to be integrated into the latest medical sciences. It can also help with certain chronic disorders and syndromes, for which the exact cause is not known so far.

2. Methods

2.1. Search strategy

The investigation was done based on databases of Scopus, PubMed, and Google Scholar, to find peer-reviewed articles that popped up between 2000 and 2024. We used the search terms including "black bile," "melancholia," "humoral theory," "oxidative stress," or "ROS," and "chronic disease." Out of the first thousand articles that were found, 135 were selected for a full read, all based on how relevant they were to the historical significance of black bile and the modern implications of oxidative stress in medicine. After some more digging, we ended up with 14 articles that made the cut for our final analysis.

In this review, we take a closer look at how black bile connects with oxidative stress in today's biomedical science. We're especially interested in how both of these ideas impact chronic diseases. Plus, we'll explore how dietary choices and lifestyle tweaks from both traditional and modern perspectives tackle these internal issues.

2.2. Inclusion criteria

1. We wanted articles that talked about black bile in those traditional medical texts.
2. Studies that linked black bile to contemporary medical issues like depression, oxidative stress, and chronic inflammation were a must.
3. Research focusing on dietary and lifestyle changes aimed at balancing those humoral imbalances and cutting down oxidative stress also made the list.

2.3. Exclusion criteria

. If an article just ranged on about other humors without mentioning black bile, it wouldn't be selected.
2. We also skipped studies that didn't directly relate to modern health practices or medical conditions.

3. Results

3.1. Black bile in ancient medicine

Black bile was one of four essential humors in ancient Greek and Persian medicine that was thought to influence mental as well as physical health. Excess black bile was said to be dry and cold and was related to melancholia, a state of depression or sadness, and digestive disorders (2, 15). It was thought that chronic illnesses such as insomnia, anxiety, digestive disorders, sluggishness of the body, and even cancer might develop due to the imbalance of black bile. Excess black bile was also thought to dull the mind and mental acuity with depression-like symptoms as we now know them. Avicenna specifically emphasized the relationship of black bile with mental fitness and wrote that when it accumulates in the brain, it generates melancholia and drowsiness (15, 16).

The treatment of excessive black bile was primarily dietary adjustments and herbs. Lemon balm (*Melissa officinalis*) and lavender (*Lavandula angustifolia*) were of considerable worth in ancient Persian medicine due to their ability to induce mental acuity (17, 18). These herbs were believed to remove "brain Sauda" (black bile of the brain) and worked as tonics to restore mental function and treat melancholia (2, 3). *Adiantum capillus-veneris* and *Fumaria officinalis* were also used to remove black bile from the body with benefits for the respiratory and gastrointestinal systems (2, 19, 20). Foods were also categorized based on their effect on the humors, with some foods being melancholic and hence subject to restriction due to their ability to induce production of black bile. Certain foods like lentils (*Lens culinaris*), camel meat (*Camelus dromedarius*), and buffalo meat (*Bubalus bubalis*) were specifically prohibited for intake by physicians due to their ability to induce melancholia and gastrointestinal ailments (20-22). Spicy foods and fatty foods, as well as processed foods like potato chips and biscuits, were also melancholic and were restricted in the diet of black bile imbal-

anced persons. In other words, certain foods in traditional medicine were recognized to have melancholic activity. Lentils were regarded as being cold and dry and hence prone to cause melancholia. In the same way, camel meat and buffalo meat were also regarded as being of cold and dry nature and hence prone to cause melancholia. Salty cheese and fast foods were believed to cause an excess of black bile and, hence, melancholic disturbances (23). Warm foods and moist foods were also popular because they were believed to melt and counteract the effect of black bile. Herbs like saffron (*Crocus sativus*), rose petals, lemon balm, lavender, and basil were thought to purify the mind and bring about mental clearness (2, 3). Warm baths and massage therapy were also commonly prescribed as lifestyle routines to encourage circulation and prevent black bile from getting stuck in the body (22, 24). Cupping was also proposed at times to treat humoral imbalances in the tradition of Persian medicine. That being said, cupping was not appropriate for evacuating black bile because it is thick in consistency and difficult to expel through this method (3, 24). Instead, treatments for excessive black bile typically involved the consumption of natural foods, particularly warm moist foods that opposed the dry and cold nature of black bile. Foods like soups and stews and herbs like mint, basil, and rosewater were prescribed to lower black bile levels and alleviate symptoms (20, 24).

3.2. Physical and herbal remedies: Traditional knowledge and contemporary science

Herbal medicines also had an influential role to play in the management of black bile in traditional medicine, and most of them are even valued for their medicinal properties in the present day. Basil, mint, rosewater, and other such herbs were widely used to counteract the dryness and coldness of black bile. It is important to clarify that the therapeutic action of these plants in TPM is holistic and attributed to their "quality" (e.g., warm and moist), which aligns with a multi-target mechanism of action. Modern science reveals that beyond antioxidant activity, these plants contain a complex mixture of bioactive compounds that influence various receptors and pathways. For instance, *Melissa officinalis* (Lemon Balm) modulates GABAergic pathways, which is crucial for its anxiolytic and mood-stabilizing effects, consistent with its traditional use for "brain Sauda" (25). Similarly, linalool in lavender acts on NMDA receptors and voltage-gated calcium channels, providing a mechanistic basis for its neuroprotective and calming properties beyond mere antioxidant capacity (26). Therefore, the parallel is not that antioxidants are the sole correlate of black bile remedies, but that the multi-faceted, systemic actions of these traditional herbs, which include antioxidant and anti-inflammatory effects, effectively address the multi-system pathologies associated with both black bile imbalance and oxidative stress.) Modern science has also established that such plants contain antioxidants that counteract oxidative stress and inflammation and demonstrate their continued applicability in the management of chronic diseases (24, 27). Ancient Persian physicians also advocated the use of physical treatments like cupping, massage, and bathing to stimulate blood circulation and avoid the accumulation of black bile within the body. It should be noted, however, that cupping was not effective in evacuating thick humors like black bile because it was not effective in evacuating them from the body (3). Cupping was instead effective for the management of excess blood or phlegm, while dietary and herbal interventions were the preferred method for the management of black bile imbalances (2, 28).

The growing consumption of natural bioactive compounds, particularly phytochemicals, for disease prevention and management has also been accountable for the popularity of nutraceuticals and functional foods. Nutraceuticals are particularly remarkable for their natural presence in food and health-promoting

activity with the primary function of health maintenance and disease prevention (29). There is also growing enthusiasm in contemporary integrative medicine for the combining of traditional herbal medicines with novel antioxidant therapies for chronic disease management associated with oxidative stress. Turmeric, green tea, and ginger are some of the plants that have been extensively explored for their anti-inflammatory and antioxidant activities and for their potential to offer new avenues of therapy that bring together ancient and modern medicine (30-32). This integrated perspective emphasizes the timeless relevance of ancient herbal knowledge that continues to impact modern therapies for oxidative stress and chronic inflammation.

3.3. Oxidative stress in modern medicine

Oxidative stress in modern medical science is an imbalance in the generation of ROS associated with the etiology of most chronic diseases such as neurodegenerative disease, mood disorders, and cardiovascular disease (6, 7). ROS (including lipid peroxides, superoxide (i.e., O^{2-} •), hydrogen peroxide (i.e., H_2O_2), and peroxyl radicals (i.e., ROO•) are electron-transfer molecules of reactive oxygen. Lipid peroxides are lipid peroxidation products and ultimately cause ferroptosis (the iron-dependent cell demise). Superoxide can react with nitric oxide to yield peroxynitrite (that is ONOO-) in the mitochondrial electron transport chain. Hydrogen peroxide, which is the product of superoxide, has a role in protein oxidation but can cause oxidative stress when it is present in high quantities. The most reactive ROS are peroxyl radicals which are produced from H_2O_2 through specific reaction (8).

Chronic inflammatory diseases including atherosclerosis, rheumatoid arthritis, inflammatory bowel disease (IBD), Alzheimer's disease, and Parkinson's disease are strongly associated with, and exacerbated by, oxidative stress (9, 32). It has been proven to be one of the root causes of mental diseases including anxiety and depression. Elevated ROS have been shown to influence the function of mood-controlling neurotransmitters including serotonin and dopamine. Neuroinflammation due to oxidative stress has been implicated in depression and consequently oxidative stress with mental disease (33, 34). Oxidative stress is a confirmed contributor to the pathogenesis of chronic inflammatory disorders. ROS cause cellular damage and also start inflammatory pathways accountable for the etiology of diabetes, atherosclerosis, and neurodegenerative disorders (6, 32).

Diets are also a major part of traditional and modern medical therapy for black bile and oxidative stress. In traditional Persian medicine, lentils, buffalo meat, and camel meat as well as processed foods such as pizza cheese, mayonnaise, and salty cheese were all classified as melancholic since they were thought to induce the accumulation of black bile (20, 21). Similarly, modern medical research also warns against using processed foods and high-fat content food since they have been shown to rise chronic inflammation and oxidative stress (Figure 1) (30, 31).

3.4. Modern dietary recommendations for reducing oxidative stress

• Fruits and Vegetables: Modern nutritional science recommends the consumption of antioxidant foods such as blueberries, green tea, and spinach. They contain polyphenols and flavonoids with antioxidant activity that neutralizes ROS and inhibits inflammation (27, 35). The antioxidant activity of flavonoids occurs through metal ion chelation and radical scavenging. It depends on the active functional group and hydroxyl groups of the phytochemicals. They inhibit the production of ROS and shield lipids against oxidative stress. Phytochemical action in cancer growth is multifaceted, as it can scavenge ROS and induce oxidative stress to hinder the growth of cancer cells based on cell class and concentra-

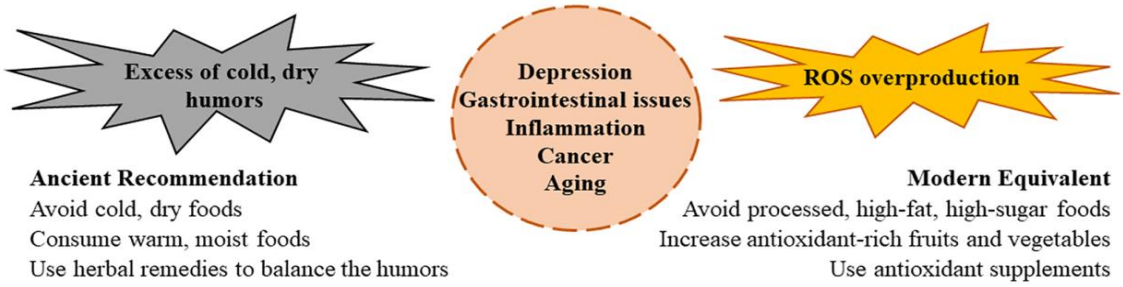

Figure 1. Comparative effects of excess black bile and reactive oxygen species (ROS) overproduction.

tion (29).

• Herbal Medicines: Classic herbs which have been employed for the management of black bile (such as basil and mint), contain bioactive compounds such as eugenol and linalool, which are considerable anti-inflammatory and antioxidant agents. These herbs are now well-recognized for balancing oxidative stress (3, 24).

• Processed Food Restriction: Ancient physicians cautioned against the consumption of melancholic foods, and similarly, modern dietary advice also aims at reducing the intake of high fat/ salt processed foods since they cause oxidative stress and inflammation (32, 36).

4. Discussion

Integrative medicine, a branch of medicine combining traditional wisdom with modern knowledge, offers favorable strategies for treatment of chronic complications. Functional foods in Persian medicine were classified based on the four qualities related to the humors. Thus, specific diets were advised to balance the body humors. Cold and dry foods (such as lentils and salty cheeses), being melancholic foods, were avoided in patients with an excess of black bile. On the other hand, warm and humid foods such as soups were proposed to counteract black bile's cold and dry nature (2, 20). Modern medicine proposes limiting oxidative stress by elevating antioxidant foods such as fruits and vegetables rich in polyphenol and flavonoids, which neutralizes ROS and protects cells from damage (27, 35). Modern dietary advice to avoid processed foods, fatty foods, and sweets (that cause inflammation and oxidative stress) resonates with ancient advice to avoid melancholic foods (that cause an increase in black bile) (30, 31). Ancient physicians also employed herbal medicines such as basil, mint, and rosewater to restrict the power of black bile. These plants and their phytochemicals possess antioxidant and anti-inflammatory activities and are still employed in restricting oxidative stress (3, 24, 37, 38).

During ancient Persian medicine, dietary modifications and warm sitz baths along with herbal medicines were suggested to reduce black bile and treat melancholic disorders in an effective manner. Some herbs were also suggested for eliminating black bile. For instance, Lemon Balm removes brain Sauda, ensures clearness of the mind and relaxation, and neutralizes black bile in the brain. Lavender is a brain tonic and removes melancholia and black bile in the brain. Adiantum (Maidenhair Fern) traditionally removes black bile and ensures respiratory and digestive health. Fumitory removes black bile and regulates production of the bile and ensures digestive health. Saffron removes cold-dry humor, cleanses the mind, and removes symptoms of black bile in the brain. Basil ensures balance

in the humors and removes black bile and aids in digestion and clearness of the mind. Damask rose petals remove black bile and ensure emotional balance and clearness of the mind. Today, the interventions are replicated in current medical suggestions where antioxidant diets rich in antioxidants, anti-inflammatory foods, and life style changes (e.g., stress management practices) are used to reduce oxidative stress and inflammation (31, 32). For instance, a recent study examined the potential of the natural flavonoid luteolin in improving irritable bowel syndrome in a rat model. Findings indicate it significantly reduces ROS levels and alleviates excessive colonic motility in a water avoidance stress model. In addition, the upregulation of heme oxygenase-1 and nuclear factor erythroid 2-related factor 2 by luteolin facilitates the translocation of Nrf2 into the nucleus and significantly attenuates hydrogen peroxide (H_2O_2)-induced oxidative damage in intestinal epithelial cells (39).

The analogy between ancient humoral theory and oxidative stress in modern biomedical science helps us understand how each system thinks of the development and management of chronic disease. Despite the fact that humoral medical theories have been largely displaced by modern science, the analogy between black bile and oxidative stress is striking. Both are conceived as underlying imbalances that, if left unadjusted, lead to systemic dysfunction, most prominently in the mind and gut (22, 32). Excess black bile in ancient times produced melancholia in the sense of sadness, drowsiness, and digestive issues. Similarly, modern studies have established oxidative stress as an important contributor to the onset of depression and anxiety disorders, diseases with striking similarities to melancholia in humoral theory. In each system, disorders of mood are thought of as brought on by an internal imbalance --- black bile in ancient times and oxidative stress in modern contexts (32, 34). Furthermore, black bile and oxidative stress are also linked to chronic inflammation. In other words, black bile in ancient times was believed to disrupt the internal balance by accumulating in different organs of the body and causing respective health issues. In modern science, oxidative stress is a catalyst of a sort for inflammation, exacerbating chronic diseases such as cardiovascular disease, diabetes, and neurodegenerative disease (32, 40). Despite the differences in medical philosophy, each system recognizes the fact that the imbalances have to be addressed in order to prevent disease progression.

4.1. Mental health: From melancholia to depression

Melancholia in traditional medicine is an excess of black bile leading to mental health disorders such as anxiety, lethargy, and sadness (2, 16). This idea fits with modern conceptions in which oxidative stress and inflammation are set up as prime causes of mood disorders (32, 34). It is notable that depression increasingly is thought to be an illness caused by neuroinflammation due to excessive ROS levels. Oxidative stress could disrupt neurotransmitter systems such as those involving serotonin and dopamine and lead to depressive symptoms and imbalance in mood. This fits with the ancient concept that excessive black bile in the brain could cause melancholia by disrupting clear-headedness and emotional balance (32, 33). Depression in modern times could be treated by combining antioxidant diets, exercise, and life changes to decrease oxidative stress and improve overall mental health. In ancient times, melancholia could be treated by dietary changes similar to those mentioned above, herbal remedies, and physical therapies such as massage and warm sitz baths to bring balance to the mind and body (2, 3).

4.2. Gastrointestinal health and chronic diseases

Black bile and oxidative stress have been involved in gut health in their respective

medical traditions. In ancient humoral theory, excessive black bile led to digestive issues such as indigestion, bloating, and constipation. Lentils, salty cheeses, and fast foods were avoided as they promoted black bile and warm and humid foods were recommended to treat gastrointestinal symptoms (21, 22). In TPM, a person with black bile imbalance is predisposed to certain patterns of dysfunction, just as in modern medicine, a person with genetic and environmental risk factors is predisposed to IBD. The key insight is that both systems identify a similar cluster of symptoms and target them with similar dietary strategies (e.g., avoiding pro-inflammatory foods like lentils, which are also high-FODMAP, and embracing soothing, antioxidant-rich broths and herbs). In modern medicine, oxidative stress has been involved in the etiology of gastrointestinal disorders such as IBD, IBS, and gastritis. ROS kills the mucosal layer of the gut and results in impaired digestion and chronic inflammation (9, 40). Modern therapy typically prescribes anti-inflammatory diets and antioxidant supplements to treat oxidative stress and recover the gut. This conceptually parallels ancient Persian dietary therapy in trying to balance black bile by eating gut-friendly foods such as broths and herbal infusions, which quietened the gut and relieved symptoms of indigestion (2, 3). For instance, due to the success of the low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (also known as FODMAP) diet in alleviating symptoms of IBS, it is advisable to avoid lentils as they contain a high FODMAP level and exacerbate gut discomfort and inflammation (41).

4.3. Cancer: From traditional beliefs to modern therapies

By drawing this parallel, we can see that TPM's approach to managing black bile through diet and lifestyle interventions to balance humors may align with modern strategies for reducing oxidative stress and cancer risk. Antioxidant-rich foods and herbs, recommended in TPM, serve a similar purpose in neutralizing ROS, thereby preventing the damage associated with cancer development (42, 43). They are thought to be imbalances leading to chronic diseases (44, 45). Polyphenols modulate carcinogenesis, proliferation and death of cells, inflammation, angiogenesis, and drug resistance by protecting against DNA damage and modulating key pathways such as MAPK and mTOR/AKT. Resveratrol modulates the MAPK pathway and influences proliferation and apoptosis of cells. Phytochemicals modulate miRNAs, inhibit NF-κB activation, inhibit the JAK/STAT pathway, and induce apoptosis. Antioxidant phytochemicals curcumin and resveratrol modulate tumor stem cells and induce death and arrest in the cell cycle. Lycopene is associated with reduced tumor incidence and increased apoptosis in breast cancer. Polyphenols induce death in cells by binding to proteins such as Bcl-2 and disrupting the cytoskeleton, and cocoa polyphenols induce pro-apoptotic proteins such as caspase 3 (29). The traditional medicine theory of black bile echoes the complex biological and phytochemical interactions in ROS and cancer pathways. The convergence of Persian medicine with modern evidence-based studies highlights the evolving nature of medical knowledge and its enduring relevance.

4.4. Implications for personalized medicine

The parallels between black bile and oxidative stress suggest that modern personalized medicine could benefit from integrating traditional dietary practices with contemporary scientific insights. Treatments in humoral theory were individualized based on an individual's temperament and humoral balance. Similarly, personalized medicine today entails individualized therapy based on an individual's genetic, environmental, and life style factors (31, 46). Incorporation of traditional dietary recommendations such as avoiding melancholic foods and consumption of herbal

teas into modern therapy regimens can allow health professionals to have more integrated approaches to treat chronic diseases such as depression, IBD, and chronic inflammation. Further, it may de-mystify more integrated therapy regimens to treat oxidative stress-related diseases.

5. Conclusion

Examination of ROS pathways may be a holistic integrated strategy for humoral medicine and indeed for black bile. This concept synthesizes ancient medical wisdom and modern psycho-neuro-endocrino-immunology and suggests the interfacing nature of psychological, neural, endocrine, and immune function. For instance, recent findings suggest indirect causation of cancer by chronic psychological stress by weakening the immune system. In ancient medicine, black bile has been associated with melancholia, depression, and tumors. Therefore, investigating ROS pathways may deepen the understanding of these ancient theories and their applicability to modern medical practices.

This review has demonstrated that ancient humoral theories, particularly the concept of black bile, still hold relevance in modern medical contexts, particularly when viewed through the lens of oxidative stress. An excess of black bile may indicate an imbalance in the body, attributed to the combustion of humors in TPM. Also, ROS overproduction is linked to harmful oxidative processes that disturb various body functions. The parallels between oxidative stress and black bile suggest that combining ancient and contemporary scientific practices could lead to new integrative therapies that reveal the underlying causes of disorders of the mind and of the gut and chronic diseases such as cancer, an emerging global health issue with rising morbidity and mortality rates. Clinical trials in the future should be directed towards investigating the benefits of the integration of the two systems of conventional and traditional medicine in oxidative conditions---regimens and lifestyles as precursors to the prevention and management of chronic diseases. Investigating the molecular pathways influenced by traditional practices could lead to a novel outlook on managing conditions linked to oxidative stress and inflammation (27, 47).

Authors contributions

- Author M.N: Conceptualization, Methodology, Writing - Original Draft
- Author A.A.M: Data Curation, Writing - Review & Editing
- Author Gh.M: Data Curation, Writing - Review & Editing, Project Supervision

Acknowledgements

The authors would like to express their gratitude to Shiraz University of Medical Sciences, Shiraz, Iran.

Availability of Data and Material

The data and materials supporting the conclusions of this study are available from the corresponding author upon reasonable request.

Funding

This research was funded by Shiraz University of Medical Sciences, under grant number 31709

Conflict of Interest

The authors declare that they have no conflict of interest.

Note

Certain parts of this article have been edited with the assistance of AI tools, including GPT, to enhance clarity and accuracy. Finally, the authors thoroughly reviewed and edited the content to ensure its quality and alignment with their vision.

References

1. Dallaire JA, Field N, Mason GJ. Activity and enrichment use in disabled Asiatic black bears (Ursus thibetanus) rescued from bile farms. *Anim Welf*. 2008;21(2):167-76.
2. Khademi A, Mansuri P, Pahlevan D, Bozorgi M, Nasiri M, Hejazi S, *et al*. Efficacy of pumpkin ointment in treatment of chronic hand eczema: A randomized, active-controlled, double blind clinical trial. *Iran J Public Health*. 2020;49(7):1339-47. doi:10.18502/ijph.v49i7.3588
3. Ghaffari F, Naseri M, Asghari B, *et al*. Spinal traumas and their treatments according to Avicenna's Canon of Medicine. *World Neurosurg.* 2015;84(1):173-7.
4. Halliwell B. Antioxidants in human health and disease. *Annu Rev Nutr.* 1996;16:33-50. doi:10.1146/annurev.nu.16.070196.000341
5. Young IS, Woodside JV. Antioxidants in health and disease. *J Clin Pathol.* 2001;54(3):176-86. doi:10.1136/jcp.54.3.176
6. De la Fuente M, Victor VM. Anti-oxidants as modulators of immune function. *Immunol Cell Biol.* 2000;78(1):49-54. doi:10.1046/j.1440-1711.2000.00884.x
7. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chem Biol Interact*. 2006;160(1):1-40. doi:10.1016/j.cbi.2005.12.009
8. Harris IS, DeNicola GM. The complex interplay between antioxidants and ROS in cancer. *Trends Cell Biol.* 2020;30(6):440-51. doi:10.1016/j.tcb.2020.03.002
9. Dröge W. Free radicals in the physiological control of cell function. *Physiol Rev.* 2002;82(1):47-95. doi:10.1152/physrev.00018.2001
10. Iqbal MJ, Kabeer A, Abbas Z, Siddiqui HA, Calina D, Sharifi-Rad J, *et al*. Interplay of oxidative stress, cellular communication and signaling pathways in cancer. *Cell Commun Signal.* 2024;22(1):7. Published 2024 Jan 2. doi:10.1186/s12964-023-01398-5
11. Zhao Y, Feng HM, Yan WJ, Qin Y. Identification of the signature genes and network of reactive oxygen species related genes and DNA repair genes in Lung Adenocarcinoma. *Front Med (Lausanne)*. 2022;9:833829. doi:10.3389/fmed.2022.833829
12. Wu K, El Zowalaty AE, Sayin VI, Papagiannakopoulos T. The pleiotropic functions of reactive oxygen species in cancer. *Nat Cancer.* 2024;5(3):384-99. doi:10.1038/s43018-024-00738-9
13. Zareian MA, Rafiee S, Yargholi A, Ahmadi M, Shirbeigi L, Nejatbakhsh F. Concept of food in Persian medicine. *Trad Integr Med.* 2022;7(3):350-6.
14. Zimmer V. Black versus Clear (f.k.a. White) Bile. *Am J Med Sci*. 2021;361(2):e11-2.
15. Schütrumpf E. Excessive mixture of black bile. In: Blamberger G, Kellerer S, Klemm T, Söffner J, editors. Sind alle Denker traurig? Fallstudien zum melancholischen Grund des Schöpferischen in Asien und Europa. Paderborn: Wilhelm Fink Verlag; 2015.
16. Vickers A, Zollman C. ABC of complementary medicine: herbal medicine. *BMJ*. 1999;319(7216):1050-3. doi:10.1136/bmj.319.7216.1050
17. Akrami R, Hashempur M H, Tavakoli A, Nimrouzi M, Sayadi M, *et al*. Effects of Fumaria parviflora L on Uremic Pruritus in hemodialysis patients: A randomized, double-blind, placebo-controlled trial. *Jundishapur J Nat Pharm Prod*. 2016;12:39744
18. Salehi-Pourmehr H, Ostadrahimi A, Ebrahimpour-Mirzarezaei M, Farshbaf-Khalili A. Does aromatherapy with lavender affect physical and psychological symptoms of menopausal women? A systematic review and meta-analysis. *Complement Ther Clin Pract*. 2020;39:101150. doi:10.1016/j.ctcp.2020.101150
19. Akbar S. Adiantum venustum G. Don./ Adiantum capillus-veneris L. (Pteridaceae). In: Handbook of 200 medicinal plants: A comprehensive review of their traditional medical uses and scientific justifications. Cham: Springer; 2020. p. 103-7.
20. Akbari A, Nasiri K, Heydari M, Nimrouzi M, Afsar T. Ameliorating potential of

ginger (Zingiber officinale Roscoe) extract on liver function and oxidative stress induced by ethanol in male rats. *Zahedan J Res Med Sci*. 2019;21(2):86464.
21. Jones JD, Zollman PE. Black bear (Ursus americanus) bile composition: seasonal changes. *Comp Biochem Physiol C Pharmacol Toxicol Endocrinol*. 1997;118(3):387-90. doi:10.1016/s0742-8413(97)00176-x
22. Radden J. Black bile and melancholia: Avicenna. In: Radden J, editor. The nature of melancholy: from Aristotle to Kristeva. New York: Oxford University Press; 2002. p. 75-8
23. Yavari M. Introduction: Hot and cold theory, the path towards personalized medicine. *Adv Exp Med Biol.* 2021;1343:1-3. doi:10.1007/978-3-030-80983-6_1
24. Patwardhan B, Warude D, Pushpangadan P, Bhatt N. Ayurveda and traditional Chinese medicine: a comparative overview. *Evid Based Complement Alternat Med.* 2005;2(4):465-73. doi:10.1093/ecam/neh140
25. Awad R, Levac D, Cybulska P, Merali Z, Trudeau VL, Arnason JT. Effects of traditionally used anxiolytic botanicals on enzymes of the gamma-aminobutyric acid (GABA) system. *Can J Physiol Pharmacol.* 2007;85(9):933-42. doi:10.1139/Y07-083
26. López V, Nielsen B, Solas M, Ramírez MJ, Jäger AK. Exploring pharmacological mechanisms of lavender (Lavandula angustifolia) essential oil on central nervous system targets. *Front Pharmacol.* 2017;8:280.
27. Pisoschi AM, Pop A. The role of antioxidants in the chemistry of oxidative stress: A review. *Eur J Med Chem.* 2015;97:55-74. doi:10.1016/j.ejmech.2015.04.040
28. Patwardhan B, Mashelkar RA. Traditional medicine-inspired approaches to drug discovery: can Ayurveda show the way forward?. *Drug Discov Today.* 2009;14(15-16):804-11. doi:10.1016/j.drudis.2009.05.009
29. Adnan M, Patel M, Snoussi M, editors. Ethnobotany and ethnopharmacology of medicinal and aromatic plants: steps towards drug discovery. *Boca Raton: CRC Press*; 2023. doi:10.1201/b22842.
30. Rahbar M, Zarei A, Ranjbar M, Tabarrai M, Shirbeigi L. Etiology, clinical manifestation and natural treatments of psoriasis from the perspective of Persian medicine. *Tradit Integr Med.* 2020;5(4):221-9. doi:10.18502/tim.v5i4.5168
31. Stewart KA. The diseases caused by black bile. In: Stewart KA. Galen's theory of black bile: Hippocratic tradition, manipulation, innovation. Leiden: Brill; 2018:129-48.
32. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol.* 2007;39(1):44-84. doi:10.1016/j.biocel.2006.07.001
33. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. *Nature.* 2000;408(6809):239-47. doi:10.1038/35041687
34. Malhi GS, Yatham LN. Bipolar and beyond: "black bile and blessings to Bedlam and brain biology". *Acta Psychiatr Scand*. 2004;110:5-6.
35. Pandey KB, Mishra N, Rizvi SI. Protective role of myricetin on markers of oxidative stress in human erythrocytes subjected to oxidative stress. *Nat Prod Commun.* 2009;4(2):221-6
36. Raskin I, Ribnicky DM, Komarnytsky S, Ilic N, Poulev A, Borisjuk N, *et al.* Plants and human health in the twenty-first century. *Trends Biotechnol.* 2002;20(12):522-31. doi:10.1016/s0167-7799(02)02080-2
37. Cioanca O, Morariu ID, Hritcu L. Natural antioxidants for the prevention and treatment of cancer. In: Chakraborti S, editor. Handbook of oxidative stress in cancer: therapeutic aspects. Singapore: Springer; 2022:277-89.
38. Shobha RI, Rajeshwari CU, Andallu B. Oxidative stress and antioxidant herbs and spices in cancer prevention. In: Preedy VR, editor. Cancer: oxidative stress and dietary antioxidants. San Diego: Academic Press/Elsevier; 2014:91-100.
39. Xia Y, Tan W, Yuan F, Lin M, Luo H.

Luteolin attenuates oxidative stress and colonic hypermobility in water avoidance stress rats by activating the Nrf2 signaling pathway. *Mol Nutr Food Res*. 2024;68(1):e2300126. doi: 10.1002/mnfr.202300126. Epub 2023 Nov 30. PMID: 38037466.

40. Fang YZ, Yang S, Wu G. Free radicals, antioxidants, and nutrition. *Nutrition*. 2002;18(10):872-9. doi: 10.1016/s0899-9007(02)00916-4. PMID: 12361782.
41. Manning LP, Yao CK, Biesiekierski JR. Therapy of IBS: Is a Low FODMAP Diet the Answer? *Front Psychiatry.* 2020;11:865. doi: 10.3389/fpsyt.2020.00865. PMID: 33110411; PMCID: PMC7488954.
42. Chugh NA, Koul A. Reactive oxygen species–mediated cancer progression and metastasis. In: Chakraborti S, Ray BK, Roychoudhury S, editors. Handbook of oxidative stress in cancer: mechanistic aspects. Singapore: Springer; 2022. doi:10.1007/978-981-15-9411-3_160
43. Singh, R. Manna PP. Reactive oxygen species in cancer progression and its role in therapeutics. *Explor Med*. 2022;3(1):43-57.
44. Tipton J. Black bile, manic depression and melancholy: two pillars of our understanding. *Med Res Arch.* 2021;9(4). doi:10.18103/mra.v9i4.2363
45. Widmer DA. Black bile and psychomotor retardation: shades of melancholia in Dante's Inferno. *J Hist Neurosci.* 2004;13(1):91-101. doi: 10.1080/09647040490885529. PMID: 15370340.
46. Kordafshari G, Ardakani MRS, Keshavarz M, Esfahani MM, Nazem E, Moghimi M, *et al*. The role of phlebotomy (Fasd) and wet cupping (Hijamat) to manage dizziness and vertigo from the viewpoint of persian medicine. *J Evid Based Complementary Altern Med.* 2017;22(3):369-373. doi: 10.1177/2156587216672757. Epub 2016 Oct 20. PMID: 30208737; PMCID: PMC5871156.
47. Uttara B, Singh AV, Zamboni P, Mahajan RT. Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. *Curr Neuropharmacol.* 2009;7(1):65-74. doi: 10.2174/157015909787602823. PMID: 19721819; PMCID: PMC2724665.