

PHARMACEUTICAL MICROBIOLOGY

New and Traditional Approaches

Editör: Doç.Dr. Şükran ÖZTÜRK

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**Pharmaceutical Microbiology: New and
Traditional Approaches**

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"Bu kitapta yer alan bölümlerde kullanılan kaynakların, görüşlerin, bulguların, sonuçların, tablo, şekil, resim ve her türlü içeriğin sorumluluğu yazar veya yazarlarına ait olup ulusal ve uluslararası telif haklarına konu olabilecek mali ve hukuki sorumluluk da yazarlara aittir."

TRADITIONAL AND COMPLEMENTARY MEDICINE APPROACHES FOR THE TREATMENT OF INFECTIOUS DISEASES AND MICROBIOLOGICAL CONDITIONS

Tuba UNVER¹

1. INTRODUCTION

Infectious diseases are one of the most common and dangerous health problems threatening human health. Throughout history, different cultures and civilizations have developed various treatment methods to combat these diseases. Before the development of modern medicine, herbal medicines, acupuncture, homeopathy, and similar traditional treatment methods were widely used. Today, these traditional methods are considered complementary and alternative medicine practices and are used alongside modern medicine (1,2). Understanding the role of traditional and complementary medicine in infectious diseases is of great importance, both historically and in current practice. The roots of traditional medicine go back thousands of years, and the accumulated knowledge in this field has made significant contributions to the development of modern medicine. In particular, herbal treatments and natural products have become the focus of renewed interest today, with the increasing antibiotic resistance (1,2).

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2. METHODS USED IN TRADITIONAL AND COMPLEMENTARY MEDICINE FOR THE TREATMENT OF INFECTIOUS DISEASES

Infectious diseases are illnesses caused by the entry and multiplication of microorganisms in the body, and their treatment is usually done with pharmaceutical agents such as antibiotics or antiviral drugs. However, many methods are used in traditional and complementary medicine to treat infectious diseases (3). Some of these methods are phytotherapy, aromatherapy, homeopathy, acupuncture, ayurveda and ozone therapy.

2.1. Phytotherapy

Phytotherapy is a medical practice related to the use of plants for therapeutic purposes. This method is based on medicinal plants and generally involves plant materials such as extracts, leaves, flowers, roots, or seeds (4). Phytotherapy has been widely used in many cultures since ancient times and is a treatment method preferred by many people today (5).

Respiratory Tract Infections: This is one of the areas where phytotherapy is commonly used. It can shorten the duration of a cold with its immune-boosting effect. Ginger (*Zingiber officinale*) alleviates flu and cold symptoms with its antiviral properties (6), while thyme (*Thymus herba*) treats respiratory tract infections with its antimicrobial properties. These plants are generally used in the form of herbal teas, tinctures, or steam inhalation (7).

Digestive System Disorders: Digestive system disorders include nausea, indigestion, irritable bowel syndrome (IBS), and constipation. Plants such as mint, turmeric, and chamomile are used in these types of disorders. Peppermint (*Mentha*) relieves nausea and gas, turmeric (*Curcuma longa*) supports digestive health with its anti-inflammatory properties, and chamomile (*Matricaria chamomilla*) can relieve stomach spasms and

indigestion. These herbs are generally used in the form of herbal teas, capsules, or tinctures (8).

Skin problems: Skin problems include acne, eczema, fungal infections, and burns. *Aloe vera*, tea tree (*Melaleuca alternifolia*) oil, and St. John's wort (*Hypericum perforatum*) are used for these types of problems (9). *Aloe vera* accelerates the healing of burns and skin irritations (10). Tea tree oil treats acne and fungal infections with its antiseptic and antifungal properties, while St. John's wort supports the healing of skin wounds. These herbs can generally be applied in the form of ointments, creams, or oils (11). Inflammatory and autoimmune diseases include arthritis, lupus, and inflammatory bowel diseases. Turmeric, ginger, and *Aloe vera* are used in these types of diseases. Turmeric reduces inflammation with its strong anti-inflammatory properties, ginger alleviates arthritis symptoms with its anti-inflammatory effects, and *Aloe vera* supports the immune system and reduces inflammation (12).

2.1.1. Various Uses of Phytotherapy

Herbal teas are prepared by brewing dried or fresh plant materials in hot water. Tinctures are liquid extracts obtained by soaking plants in alcohol or glycerin. Ointments and creams are prepared by mixing plant extracts with oil or beeswax. Essential oils are concentrated oils obtained by distilling plants and can be used in aromatherapy, steam inhalation, or applied to the skin in diluted form. Capsules and tablets are prepared by filling capsules with plant extracts or powdered plant materials (13).

There are some points to consider when using herbal medicines. It is important to use them in the correct dosage, as an overdose can lead to toxicity. Also, herbal medicines have the potential to interact with other medications, so those with chronic diseases, those taking blood thinners, or blood pressure

medication should be careful (14). Some phytotherapeutics used in the treatment of infectious diseases are listed below:

The phenolic compounds found in elderberry (*Sambucus nigra*), including kaempferol, quercetin, isoquercitrin, rutin, and chlorogenic acid, exhibit antiviral activity and possess anti-inflammatory, immunoregulatory, and antioxidant properties. Consuming two cups of elderberry flower tea daily is recommended (15).

The early-flowering summer linden (*Tilia platyphyllos*) and the winter linden (*Tilia cordata*) species, which flower about two weeks later, provide the diaphoretic effect of linden, which helps to eliminate toxins from the body through sweating (16). In addition, because they contain mucilage and tannin compounds, they can act as expectorants, especially for the chest. These components can help soothe the throat and reduce coughing (17).

Propolis is a bee product that researchers have observed to have antifungal, antimicrobial, and antiviral effects. The antimicrobial properties of propolis stem from the phenolic compounds it contains. In experiments, it was observed that propolis is effective against both gram-negative and gram-positive bacteria, but its effect against gram-negative bacteria is less. In vitro and in vivo studies have shown that propolis activates macrophages, enhances their antimicrobial properties, and stimulates antibody production (18).

Garlic (*Allium sativum*) is a plant known for its natural antibiotic properties. These properties support its use in the treatment of various infectious diseases. In particular, garlic can be effective against viral infections such as colds and flu thanks to its active compounds. The compound allicin, in particular, is thought to be effective against viruses (19).

Tea tree oil is a herbal oil with natural antibacterial, antiviral, antifungal, and anti-inflammatory properties. Because

of these properties, it can be used to treat various infectious diseases. Tea tree oil can fight bacteria, fungi, and viruses on the skin. It can be effective in treating skin conditions such as acne, fungal infections, eczema, and psoriasis (20). When applied directly to the skin, it can inhibit the growth of microorganisms in the infected area and accelerate healing. It is also commonly used to treat foot and nail infections, such as athlete's foot (21).

Ginger has strong anti-inflammatory properties that help reduce inflammation in the body. This property can help regulate the body's inflammatory response during infection. In particular, it can alleviate the inflammatory symptoms caused by viral infections such as colds and flu (22). In addition, ginger is known to have antimicrobial properties effective against many types of bacteria and viruses (23).

Echinacea is known for its immune-boosting effects. Increasing the immune system's response can make the body more resistant to infections. Therefore, it can be used especially in the treatment of colds, flu, and other viral infections (24). Echinacea is also known for its anti-inflammatory properties. This property can reduce inflammation associated with infections and may be beneficial, especially in inflammatory diseases such as upper respiratory tract infections (25).

Chamomile has anti-inflammatory and antimicrobial properties. Thanks to these properties, it can help alleviate symptoms associated with infections. It can be used especially to treat symptoms associated with infections, such as a sore throat and stomach problems. Its anti-inflammatory properties can help control symptoms caused by infections by reducing inflammation in the body (26). It can be used in forms such as a gargle or chamomile tea to help alleviate infection-related symptoms (27).

2.2. Homeopathy

The term "homeopathy" originates from the Greek. The word "homeo" means "similar" or "in a similar way," while the word "pathy" means "disease" or "suffering" (28). Homeopathy is a medical and therapeutic approach based on the principle of "treating like with like," taking into account the integrity of the individual's body and mind. Homeopathy was developed by the German physician Samuel Hahnemann in the 18th century. The basic principle of homeopathy is that a substance can cause specific symptoms in a healthy person (29). Homeopathy uses herbal, mineral, or animal substances in diluted form. These substances are called homeopathic medicines. Homeopathic medicines are usually presented in the form of granules, drops, or tablets. Homeopathy can be used to alleviate disease symptoms, strengthen the immune system, and support the balance of an individual's body, mind, and spirit (30).

Homeopathy is popular among alternative or complementary medicine practices in many countries and is used to treat a variety of health problems. The medicines used in homeopathy are called "remedies" (31). The variety of remedies used in homeopathic treatment is quite wide. These can be obtained from various sources, including animal, plant, and mineral sources, as well as acids, salts, enzymes, and synthetic substances (30,31).

Viral infections such as colds and flu usually present with nasal congestion, cough, sore throat, headache, muscle aches, and fever. Homeopathic remedies can help alleviate these symptoms and accelerate the healing process. For example, the homeopathic preparation *Oscillococcinum* can help reduce the severity of symptoms such as fever, chills, muscle aches, and weakness, and speed up the healing process (32).

The choice of homeopathic remedies is usually based on the patient's symptoms, their severity, and personal medical history. For example, when a person experiences flu symptoms, if prominent symptoms such as fever and weakness are present, the homeopathic remedy Belladonna may be recommended. Similarly, if symptoms such as cough and nasal congestion are more prominent, another homeopathic remedy (e.g., Bryonia) may be recommended (32, 33).

Homeopathic remedies are usually presented in a very diluted form, and patients typically take them in granular or dropper form. These remedies are used to alleviate symptoms and stimulate the body's self-healing ability (33).

Throat infections: These usually manifest with symptoms such as sore throat, difficulty swallowing, redness, swelling, and tonsillitis. Belladonna is a homeopathic remedy often recommended for feverish and inflamed throat infections (34). This remedy can be used in cases characterized by a sudden onset and severe sore throat (35). It can also be effective for patients with throat redness and swelling, as well as difficulty swallowing. Hepar sulfur is a homeopathic remedy recommended for inflammatory and purulent throat infections. This remedy is often used for patients with purulent tonsillitis accompanied by a sore throat and difficulty swallowing (34).

Sinusitis is a condition caused by inflammation of the sinus cavities. This condition usually manifests itself with symptoms such as nasal congestion, runny nose, facial pain and headache, fatigue, and sometimes fever (36). Silicea is a homeopathic remedy recommended for patients with sinusitis symptoms. This medicine is generally used in cases of severe sinusitis, particularly those characterized by pronounced nasal congestion and headache (37). Kali bichromicum is another homeopathic medicine used to relieve sinusitis symptoms. This

medicine is effective for sinusitis with symptoms such as thick, heavy nasal discharge, facial pain, and a sensation of pressure in the forehead and eyes. It can also relieve symptoms such as nasal congestion and cough (37).

Urinary tract infections (UTIs) are generally characterized by symptoms such as burning during urination, frequent urination, blood in the urine, abdominal pain, and cloudy urine (38). Cantharis is a homeopathic remedy frequently used to treat UTIs. This remedy is effective in patients with symptoms such as burning during urination, frequent urination, and blood in the urine (38). Staphysagria is another homeopathic remedy used in patients with specific symptoms of UTIs. This remedy is particularly effective in patients with symptoms such as intermittent burning during urination, a burning sensation in the urine, and a burning sensation in the genital area. It can also alleviate nervous or emotional stress caused by UTIs (39).

The choice of homeopathic remedies is generally based on the patient's symptoms and their severity. For example, Cantharis is generally recommended for patients with more severe UTI symptoms, while Staphysagria may be recommended for patients with more specific symptoms. Skin infections: These usually manifest as redness, swelling, increased heat, pain, itching, and pus on the skin. Calendula is a homeopathic remedy frequently used to treat skin infections. This remedy can alleviate symptoms such as redness, swelling, and increased heat in the infected areas of the skin. It can also help skin infections heal faster by accelerating the wound healing process (40). Thuja is another homeopathic remedy used in patients with specific symptoms of skin infections. This remedy is particularly effective in patients with symptoms such as warts or skin lesions caused by viral infections. It can also alleviate symptoms such as itching, pain, and tenderness on the skin (41).

2.3. Aromatherapy

Aromatherapy is a practice in which the scents of plant extracts (also known as essential oils) or the absorption of these oils through the skin or respiratory tract are used to improve health and well-being. Aromatherapy can also be used to treat or alleviate symptoms of infectious diseases. Some essential oils have antiviral, antibacterial, and antifungal properties and can therefore help in the treatment or management of infection-related symptoms (42).

The origins of aromatherapy go back to ancient civilizations. Plant extracts have been widely used for medicinal and spiritual purposes across various cultures since antiquity (43). Civilizations such as ancient Egypt, Mesopotamia, and China have documented the use of herbal oils for health, hygiene, and spiritual healing. The ancient Egyptians used plant extracts and essential oils to mummify the dead and bring peace to their souls. The use of aromatic plants for medicinal purposes was also common in Mesopotamia and China (42,43). In medieval Europe, herbal oils and plant extracts were popular for fighting and protecting against epidemic diseases. In particular, herbal oils and plant extracts were used to prevent the spread of epidemic diseases such as the Black Death (43).

The modern practice of aromatherapy gained importance in the early 20th century with the work of the French chemist and botanist René-Maurice Gattefossé. Gattefossé discovered that lavender essential oil was effective in treating burns, a significant turning point in the field of aromatherapy. Later, figures such as the French aromatherapist Dr. Jean Valnet and the English aromatherapist Marguerite Maury continued to research the effects of essential oils on health and laid the foundations of modern aromatherapy practices. Today, aromatherapy is widely used in the health field (44).

2.3.1. Application Methods of Aromatherapy

Topical Application: Essential oils are usually diluted with a carrier oil (e.g., jojoba, coconut oil) and applied directly to the skin. They can be applied by massaging into infected areas, the chest, and the back (45).

Steam Inhalation: Essential oils can be used by adding them to hot water and inhaling the steam. This method is quite effective for respiratory tract infections (46).

Diffuser Use: Essential oils can be used in diffusers to disperse them into the air. This both cleans the air and allows the oils to be effective through inhalation (47).

2.3.2. Therapeutic Applications and Biological Effects of Essential Oils

Tea tree oil (*Melaleuca alternifolia*) exhibits antibacterial and antiviral properties. It is effective against a broad spectrum of bacteria and viruses and is frequently used to manage skin infections, acne, and fungal conditions (48). Application methods include topical use in diluted form or inhalation as vapor. *Eucalyptus* oil (*Eucalyptus globulus*) is used in respiratory tract infections. Eucalyptus oil can alleviate the symptoms of colds, flu, and sinus infections. It relieves breathing by reducing mucus buildup (49). It can be used for vapor inhalation or applied topically to the chest area. Lavender oil (*Lavandula angustifolia*) possesses anti-inflammatory and calming properties. It is used to reduce stress and enhance sleep quality, and it may offer protection against skin infections (50). It can be administered as a massage oil, added to bath water, or used with a diffuser. Peppermint oil (*Mentha piperita*) has antimicrobial and analgesic effects. Peppermint oil can be used for headaches, muscle aches, and digestive problems. It is also effective against bacteria and fungi (51). It can be applied to the skin after dilution with a thin carrier oil or inhaled with a diffuser. Thyme oil (*Origanum*

vulgare) has strong antibacterial properties. Thyme oil can be particularly effective against resistant bacteria. It can be used as a supportive treatment for colds, flu, and other infections (52). It can be applied to the skin after dilution or used with a diffuser. Rosemary oil (*Rosmarinus officinalis*) has antibacterial and antifungal effects. Rosemary oil can be effective against various bacteria and fungi (53). It can be used as a steam inhalation or massage oil for respiratory tract infections. Lemon oil (*Citrus limon*) demonstrates antimicrobial activity against bacteria and viruses and is also reported to possess immune-enhancing properties (54). It may be diffused into the air or applied topically in diluted form. Clove oil (*Syzygium aromaticum*) exhibits antibacterial and antiviral properties and is particularly utilized in oral health and the management of respiratory tract infections (55). It may be administered as a mouthwash or via a diffuser. Cinnamon oil (*Cinnamomum verum*) exhibits strong antimicrobial activity against bacteria, viruses, and fungi (56). It may be diffused into the air or applied topically in diluted form. Bergamot oil (*Citrus bergamia*) has antibacterial and antiviral effects. Bergamot oil can be used to treat skin and respiratory tract infections (57). It can be used with a diffuser or added to bath water. Sage oil (*Salvia officinalis*) demonstrates antimicrobial and anti-inflammatory properties, showing efficacy against a variety of bacteria and fungi and reducing inflammation (58). It may be used as a steam inhalation or applied topically. Sandalwood oil (*Santalum album*) possesses antibacterial and antiviral properties and is used to treat skin and respiratory tract infections (59). It may be applied topically in diluted form or used with a diffuser. Chamomile oil (*Matricaria chamomilla*) exhibits anti-inflammatory and calming effects. It is used to alleviate skin irritations and reduce stress due to its relaxing properties (60). Administration methods include addition to bath water, use with a diffuser, or topical application.

2.4. Acupuncture

Acupuncture is a therapeutic practice intended to balance the flow of energy, known as Qi or Chi, within the body. Traditional Chinese medicine posits that Qi circulates through meridians, or energy channels, and that blockages or imbalances in these pathways result in disease. Acupuncture seeks to regulate Qi flow and support natural healing processes by inserting thin needles into specific points along the meridians (61).

Acupuncture is an important component of traditional Chinese medicine, which has a history spanning thousands of years. Although its origins cannot be precisely determined, acupuncture has been practiced in China since ancient times (62). According to traditional Chinese medicine, the flow of energy called "Qi" or "Chi," considered the body's life energy, must be in balance. Acupuncture is a treatment method that involves inserting thin needles into specific points to balance the body's energy flow. Acupuncture is commonly utilized for pain management, stress reduction, and general health improvement (61,62).

2.4.1. Acupuncture Techniques

Needling: The main technique of acupuncture is the insertion of thin needles into specific acupuncture points. These needles are usually disposable and sterilized, and are inserted to a certain depth under the skin. The aim of inserting the needles is to regulate the flow of Qi (energy) in the body and restore energy balance (63). **Moxibustion:** In this technique, a heated herb (usually the dried leaves of *Artemisia vulgaris*) is burned and brought close to specific acupuncture points or body areas. Heat is used to regulate the flow of Qi in the body and to provide therapeutic effects (64).

Cupping Therapy: In this technique, specially designed glass or plastic cups are applied to the skin, creating a vacuum

effect that draws the skin upward. This technique is intended to promote circulation by increasing the flow of blood and Qi beneath the skin. Cupping therapy is frequently employed to alleviate pain and inflammation (64).

Auricular acupuncture involves the insertion of needles into specific points on the ear, which is considered a micro-map of the body. As a result, auricular acupuncture may be used to address a variety of symptoms throughout the body (63). Electroacupuncture involves placing acupuncture needles beneath the skin, followed by mild electrical stimulation. This technique is intended to enhance the effects of traditional acupuncture and achieve more pronounced therapeutic outcomes (64).

Acupuncture may serve as a complementary treatment in the management of various infectious diseases. For instance, in upper respiratory tract infections such as colds and influenza, as well as respiratory system infections like bronchitis and pneumonia, acupuncture can help alleviate symptoms and reduce inflammation (65). It is also utilized to manage symptoms and control inflammation in the urinary tract, skin, and eye infections. Additionally, acupuncture has the potential to enhance immune function and support the body's overall healing processes (66,67).

2.5. Ayurveda

Ayurveda is a traditional health system that originated in India and has a history spanning thousands of years. The term "Ayurveda" means "knowledge of life" in Sanskrit, derived from "ayur" (life) and "veda" (knowledge). This holistic medical system seeks to balance human health on physical, mental, and spiritual levels (68). Essentially, Ayurveda aims to keep the human body, mind, and spirit in balance. It considers the human body to be composed of five elements that mimic the balances in the universe: earth, water, fire, air, and ether. These elements

form the three basic energies or doshas known as Vata, Pitta, and Kapha in the body (69).

Vata: Composed of the elements of air and ether, it controls movement, nervous system functions, and metabolism. Vata imbalance can cause problems such as anxiety, constipation, dry skin, and sleep disorders. Pitta: Composed of fire and water elements, it controls digestion, metabolism, skin, and mind functions. Pitta imbalance can lead to irritability, acid reflux, skin inflammations, and digestive problems. Kapha, composed of earth and water, is responsible for body structure, immune system function, and emotional stability. Imbalances in Kapha may lead to excess weight, congestion, depression, and reduced immune response (70)

According to Ayurveda, each individual's body type (prakriti) represents a unique combination of the three doshas. Achieving and maintaining balance among the doshas requires appropriate lifestyle, dietary, and environmental adjustments (69). Ayurvedic treatments are personalized based on an individual's prakriti and specific imbalances, and may include herbal remedies, dietary and lifestyle modifications, massage, yoga, meditation, and detoxification techniques (70).

2.5.1. Application of Herbal Medicines in Ayurveda for the Management of Infectious Diseases

Neem (*Azadirachta indica*) is a widely used herb in Ayurveda, recognized for its antibacterial, antiviral, and antifungal properties. Neem leaves and oil are applied externally to treat skin infections, including acne, eczema, and fungal conditions. Additionally, teas or supplements derived from Neem leaves may enhance immune function, supporting the body's ability to combat infections (71). Neem also benefits the digestive system by promoting intestinal health and protecting against intestinal infections. Furthermore, Neem sticks are traditionally

used as toothbrushes to support oral hygiene and prevent oral infections (71).

Tulsi (*Ocimum tenuiflorum*), often referred to as the "sacred herb" in Ayurveda, possesses a range of medicinal properties. Tulsi plays a significant role in the management of infectious diseases. Tea prepared from Tulsi leaves is believed to strengthen the immune system and enhance the body's defense against infections (72). Tulsi is commonly used to treat respiratory tract infections, including colds, coughs, and bronchitis, due to its antimicrobial and anti-inflammatory effects. Its antiviral properties also offer protection against influenza and other viral infections (72).

Panchakarma refers to a series of detoxification procedures designed to eliminate toxins from the body. These methods include massage, herbal oil treatments, steam baths, and bowel cleansing (73). Each Panchakarma therapy employs specific mixtures and techniques. For example, Vamana (Vomiting Therapy) utilizes ginger, lemon juice, honey, and specialized herbal medicines to stimulate the digestive system and induce vomiting. Virechana (Purgation Therapy) involves a mixture of triphala powder, castor oil, and selected herbal medicines to promote bowel movements and facilitate the elimination of toxins (74).

Yoga and Meditation: Yoga and meditation are an integral part of Ayurveda for maintaining mental and spiritual balance. Yoga improves physical flexibility and strength, while meditation calms the mind and reduces stress (75).

2.6. Ozone Therapy

Ozone therapy is a treatment method that uses ozone gas for medical purposes. Ozone is a gas composed of three oxygen atoms, represented by the formula O₃. In medical applications, ozone is particularly noteworthy for its antiviral, antimicrobial,

and anti-inflammatory properties (76). When applying ozone therapy, ozone gas is usually administered to the body using specific methods (77,78). These methods are: 1. Ozone Injection: Ozone gas is mixed into a liquid carrier substance at a specific concentration and injected directly into the infected area or specific points on the body. This method can be used to target local infections and regional problems (77). 2. Ozone Oxygen Therapy (Ozone Therapy Cabin): In this method, the patient is placed in a cabin, and ozone gas is introduced into it. The patient absorbs ozone through the skin and benefits from its effects. This method can be used to strengthen the general immune system and improve circulation (77). 3. Rectal Ozone Therapy: Ozone gas is dissolved in a sterile liquid and administered rectally. This method can be used to treat intestinal infections and strengthen the immune system (78). 4. Ozonized Water Therapy: Ozone gas is added to water to produce ozonized water using a special device. This ozonized water can be consumed or applied externally to the skin. Drinking it is generally aimed at digestive system infections and bowel cleansing (78).

Ozone therapy can potentially be effective against many different types of infections: 1. Bacterial Infections: The antimicrobial properties of ozone gas can be effective against bacterial infections. It can be used as an alternative treatment, especially against bacteria resistant to antibiotics (78). 2. Viral Infections: The antiviral properties of ozone suggest it may be effective against viruses. It can be used in the treatment or prevention of viral infections such as influenza (79). 3. Fungal Infections: It can also be effective against fungal infections. It can be used especially in the treatment of fungal infections on the skin (79).

3. CONCLUSION

This study assesses the effects and historical application of traditional and complementary medicine methods for infectious diseases. Traditional medicine has been practiced across diverse cultures for millennia and remains prevalent in the treatment of infectious diseases. Methods such as phytotherapy, homeopathy, aromatherapy, acupuncture, Ayurveda, and ozone therapy are regarded as effective and reliable approaches for managing infectious diseases.

The findings indicate that traditional and complementary medicine methods contribute meaningfully to modern medical practice. Integrating these approaches with conventional medicine offers more diverse treatment options and may enhance treatment outcomes. When used alongside modern medicine, traditional methods can improve patients' quality of life and overall health outcomes. The results underscore the significance of traditional and complementary medicine in the management of infectious diseases. Further research is necessary to evaluate the effectiveness and reliability of these methods. Nevertheless, current evidence supports their role as significant contributors and potential alternatives or adjuncts in the treatment of infectious diseases.

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TARDIGRADES: AN EVALUATION FROM THE PERSPECTIVE OF PHARMACEUTICAL MICROBIOLOGY

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1. INTRODUCTION

Adaptation mechanisms that enable survival under environmental stress conditions have become major research topics in pharmaceutical microbiology. Stressors such as oxidative stress, radiation, dehydration, temperature fluctuations, and nutrient deprivation drive organisms to develop diverse defense systems that preserve cellular integrity, providing important insights into microbial resilience, environmental adaptation, biofilm formation, and resistance development (1,2,3).

Among extremotolerant organisms, tardigrades have emerged as valuable model systems because of their ability to survive under conditions including high radiation doses, extreme temperatures, vacuum, severe water loss, and oxidative stress (4,5,6). Their remarkable resilience is associated with tardigrade-specific intrinsically disordered proteins (TDPs), DNA protection and repair systems, antioxidant defenses, and biochemical mechanisms that regulate cellular water balance. In particular, intrinsically disordered proteins contribute to the stabilization of cellular structures during dehydration, whereas DNA repair

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systems limit damage caused by radiation and oxidative stress (7,9,21,22).

From a pharmaceutical microbiology perspective, the stress responses observed in tardigrades share important functional similarities with the environmental adaptation mechanisms of microorganisms. Oxidative stress responses, DNA repair pathways, and metabolic suppression processes in tardigrades parallel the defense mechanisms found in extremotolerant and spore-forming microorganisms. For example, the genome protection systems of tardigrades exhibit functional similarities to the DNA repair mechanisms of *Deinococcus radiodurans*, while sporulation in *Bacillus* and *Clostridium* species resembles the cryptobiotic states of tardigrades (10,11,12,13). These protective mechanisms have inspired biomimetic approaches for stabilizing biological materials and preserving microbial preparations, while also raising important considerations regarding biosafety and dual-use technologies (14,15,23).

2. BIOLOGICAL CHARACTERISTICS AND EXTREME RESILIENCE MECHANISMS OF TARDIGRADES

Tardigrades are important biological models because of the multilayered defense systems they have developed to cope with environmental stress conditions (11). Understanding the cellular and molecular basis of this resilience may provide valuable insights into processes such as microbial dormancy, sporulation, biofilm-associated resistance, and environmental stress tolerance (1,3).

2.1. Taxonomic Classification and General Characteristics of Tardigrades

Tardigrades are microscopic invertebrates belonging to the phylum Tardigrada within the superphylum Ecdysozoa. They are currently classified into three main classes: Eutardigrada, Heterotardigrada, and Mesotardigrada, although most studies have focused on Eutardigrada and Heterotardigrada because information on Mesotardigrada remains limited (11,24). Eutardigrada species are predominantly found in terrestrial and freshwater habitats, whereas Heterotardigrada species are more common in marine environments (11).

Tardigrades inhabit diverse microhabitats, including mosses, lichens, soil, freshwater sediments, and marine ecosystems, reflecting their high capacity to adapt to variations in water availability, temperature, osmotic pressure, and nutrient conditions (4,11,25). Morphologically, they are characterized by a segmented body, four pairs of limbs, and a cuticular outer covering that provides structural support and serves as a protective barrier against water loss, osmotic fluctuations, and physical damage (11). Similar to protective structures in microorganisms, such as cell walls, capsules, and spore coats, these features contribute to their remarkable environmental resilience (3,13). Their ability to transition from an active state to metabolically suppressed forms while preserving cellular integrity makes tardigrades valuable biological models for understanding survival under environmental stress conditions (4,11,26).

2.2. Adaptation to Extreme Environmental Conditions

The widespread distribution of tardigrades across different ecosystems is closely related to their exceptional tolerance to environmental changes. These organisms can survive under conditions that are considered lethal for many forms of life,

including dehydration, high osmotic pressure, extreme temperature fluctuations, high hydrostatic pressure, and intense radiation (4,11,27). One of the most remarkable features of tardigrades is their ability to resume life processes when favorable conditions return, even after a substantial loss of cellular water (2,4,27).

Tardigrades also exhibit considerable tolerance to both low and high temperatures. Their ability to remain viable at temperatures far below the freezing point or after short-term exposure to high temperatures suggests the presence of protective systems that can limit stress-induced effects such as protein denaturation, membrane damage, and metabolic disturbances (5,11). Likewise, their resistance to ultraviolet and ionizing radiation indicates the existence of effective mechanisms for genome protection and repair (6,9).

These characteristics resemble the adaptation mechanisms found in microorganisms that can survive under environmental stress (1,10). Desiccation tolerance, metabolic suppression, preservation of macromolecular structures, and post-stress recovery processes are comparable to the defense strategies described in spore-forming bacteria, extremotolerant microorganisms, and certain fungal species (13). However, the remarkable resilience of tardigrades cannot be explained by a single mechanism. Instead, metabolic regulation, cryptobiotic states, protein protection systems, DNA repair mechanisms, and antioxidant defense processes work together to limit the harmful effects of environmental stress (6,7,10,11,28).

2.3. Cryptobiosis Mechanism

The remarkable tolerance of tardigrades to extreme environmental conditions is largely based on a specialized physiological state known as cryptobiosis (4,11). Cryptobiosis is an adaptive strategy in which an organism reversibly reduces its

metabolic activity to an extremely low level, and visible signs of life temporarily approach complete suspension. During this process, energy-demanding activities such as growth, development, and reproduction are suppressed, while mechanisms responsible for maintaining cellular integrity remain active (2,4,29). During cryptobiosis, metabolic activity and oxygen consumption decrease significantly, and the organism's responses to environmental changes become highly limited (4,11,29). However, when favorable conditions are restored, tardigrades can return to an active state and resume their normal biological functions (2,4).

Cryptobiosis is not a single process but occurs in different forms depending on the nature of the environmental stress. Anhydrobiosis, the best-characterized cryptobiotic state, is triggered by severe water loss and involves the transition to a compact “tun” state in which metabolic activity is reduced to a minimum and energy consumption decreases significantly (2,4,11,31). Tardigrade-specific intrinsically disordered proteins, antioxidant defense systems, and DNA protection mechanisms cooperate to preserve proteins, membranes, and genetic material during dehydration (6,7,8,10). Cryobiosis develops under freezing conditions and is associated with protective mechanisms that regulate intracellular water, stabilize macromolecules, and limit freezing-induced structural damage (5,11,16,32). Osmobiosis occurs in response to elevated osmotic pressure and involves physiological adjustments that maintain cellular water balance, sharing several protective features with desiccation tolerance mechanisms (1,2,11,33). In contrast, chemobiosis represents a less extensively studied response to chemical stressors, in which antioxidant defense systems and cellular repair processes are thought to play important protective roles against chemically induced damage (1,4,10,11).

Despite their different triggers, all forms of cryptobiosis contribute to the preservation of biological structures by reducing energy consumption and limiting cellular damage under conditions that disrupt cellular homeostasis (2,11). These strategies exhibit functional similarities to stress-tolerance mechanisms observed in bacterial spores, dormant fungal forms, and metabolically suppressed microbial populations (13). Consequently, cryptobiosis provides an important framework for understanding cellular resilience and offers valuable insights for the stabilization of biological materials, cryopreservation technologies, and the development of biomimetic approaches in pharmaceutical microbiology (13,14,30).

2.4. Cellular and Molecular Protection Mechanisms

Cryptobiosis is one of the most remarkable adaptations that tardigrades have evolved to cope with environmental stress. However, the maintenance of this state depends on the presence of coordinated protective systems operating at both cellular and molecular levels (4,11). Environmental stressors such as dehydration, freezing, radiation, osmotic imbalance, and chemical agents can induce protein denaturation, membrane disruption, oxidative damage, and genomic instability (1,2,9). The extraordinary resilience of tardigrades therefore cannot be attributed to a single mechanism but instead arises from the integrated action of multiple protection and repair pathways (6,7,11,35).

Among the most distinctive components of this protective network are tardigrade-specific intrinsically disordered proteins (TDPs), which have provided important insights into the molecular basis of desiccation tolerance (7,8,22). Unlike classical globular proteins, TDPs lack stable three-dimensional structures but can dynamically interact with cellular components under stress conditions (7,8). These proteins, including the CAHS,

SAHS, and MAHS families, contribute to cellular protection by stabilizing biomolecules, limiting protein aggregation, and promoting the formation of vitrification-like protective microenvironments under low-water conditions (7,8,17,37). Their identification has been particularly important because many tardigrade species contain only low levels of trehalose, suggesting that resilience largely depends on alternative protein-based protection systems (7,37).

Genome preservation represents another fundamental component of tardigrade resilience. Ionizing radiation, ultraviolet exposure, and oxidative stress can result in DNA strand breaks and genomic instability (1,9). Tardigrades possess effective defense systems that not only repair DNA damage but also limit its formation. A notable example is the Damage Suppressor (Dsup) protein, first identified in *Ramazzottius varieornatus*, which interacts with chromatin and protects DNA against reactive oxygen species (6,34). In addition, genomic studies have demonstrated the conservation of several DNA repair pathways, including homologous recombination, nucleotide excision repair, and base excision repair mechanisms, enabling the restoration of genome integrity following stress exposure (18,36).

Protection against environmental stress also requires effective control of reactive oxygen species. Increased ROS production during dehydration, radiation exposure, temperature fluctuations, and rehydration can damage proteins, lipids, and nucleic acids (10,38). Tardigrades counteract these effects through enzymatic and non-enzymatic antioxidant systems, including superoxide dismutase, catalase, peroxidases, glutathione, and other free-radical scavengers (10,11). The close relationship between antioxidant defenses and DNA protection systems indicates that stress tolerance depends on the coordinated limitation of both oxidative and genomic damage (6,10,18).

The preservation of protein function and membrane integrity is equally critical for long-term survival. Reduced intracellular water availability can promote protein aggregation and alter membrane organization (2,9). TDPs and vitrification-related processes are thought to create protective intracellular environments that preserve macromolecular organization and reduce molecular mobility under low-water conditions (7,19,40,41). Consequently, proteins, membranes, and genetic material remain sufficiently protected to allow biological activities to resume when favorable conditions return (11).

Collectively, these interconnected mechanisms demonstrate that tardigrade resilience emerges from an integrated protection network rather than from individual stress-response pathways. Beyond their biological significance, these systems have attracted considerable interest as models for the stabilization of biological materials and the development of biomimetic strategies aimed at improving the resilience of vaccines, protein therapeutics, enzyme preparations, probiotics, and other biopharmaceutical products (7,14).

3. MICROBIOLOGICAL ADAPTATION AND STRESS RESPONSES IN TARDIGRADES

The protective systems that tardigrades have evolved against environmental stress are not considered adaptations unique to multicellular organisms. Recent studies have shown that many of the defense mechanisms identified in these organisms are based on biological principles similar to the stress responses observed in microorganisms (1,10,13,42). Although the molecular tools involved may differ, the underlying goals are shared: preserving cellular integrity, reducing energy consumption, limiting macromolecular damage, and restarting metabolic activity when favorable conditions return (1,11,42).

From the perspective of pharmaceutical microbiology, examining these similarities is particularly important. Microbial responses to environmental stress directly influence the effectiveness of sterilization procedures, the stability of biological products, the preservation of microbial viability, and the development of resistance (3,10,13). Therefore, comparing the adaptation mechanisms identified in tardigrades with those of microbial systems can contribute to a better understanding of the fundamental biological principles that underlie stress tolerance.

3.1. Oxidative Stress and Cellular Defense

Oxidative stress arises from an imbalance between the production of reactive oxygen species (ROS) and their detoxification, leading to damage to proteins, lipids, and nucleic acids. Dehydration, radiation, temperature fluctuations, and various chemical agents are among the major environmental factors that trigger this process (1,10,43).

Under conditions of increased oxidative burden, tardigrades can limit cellular damage through highly effective antioxidant defense systems (4,11). Similarly, bacteria and fungal species reduce the effects of reactive oxygen species by increasing the production of enzymes such as superoxide dismutase, catalase, and peroxidases (10). Additional defense mechanisms, including the activation of DNA repair pathways, the removal of damaged proteins, and the synthesis of protective molecules, also contribute to stress tolerance (6,10,18,43).

Oxidative stress responses are important not only for environmental adaptation but also for host–microorganism interactions. Defense mechanisms that protect against the oxidative pressure generated by the immune system can contribute to the ability of certain microorganisms to survive within the host (10,43).

Oxidative stress is also an important factor affecting the viability and efficacy of biological products during production, drying, and storage. Therefore, understanding natural stress-tolerance mechanisms may contribute to the development of more resilient microbial preparations.

3.2. Radiation and UV Resistance

Radiation and ultraviolet (UV) light are among the major environmental stress factors that cause DNA damage (1). UV radiation induces various forms of DNA damage, particularly pyrimidine dimers, whereas ionizing radiation can produce more extensive effects, including single- and double-strand breaks, protein oxidation, and membrane damage. For this reason, radiation tolerance is considered an important model for studying cellular protection and repair mechanisms (1,12).

Tardigrades are among the organisms that have attracted considerable attention because of their remarkable resistance to radiation. Some species have been shown to remain viable even after exposure to radiation doses that are considered lethal for most animals (9,44). This tolerance depends not only on the repair of damage after it occurs but also on the protection of DNA and other cellular components from the initial effects of radiation (6,9,44).

One of the best-known examples of radiation resistance in microbiology is *Deinococcus radiodurans*. Despite extensive DNA damage caused by high doses of ionizing radiation, this bacterium can restore genome integrity through highly efficient repair systems (12,39). This capability shows functional similarities to the DNA protection and repair mechanisms identified in tardigrades (6,18). To limit UV-induced damage, microorganisms employ mechanisms such as photoreactivation, nucleotide excision repair, and various stress response pathways (12). Likewise, studies have shown that cellular damage in

tardigrades can be limited following UV exposure and that biological functions can be maintained under favorable conditions (11,18). These findings suggest that similar environmental pressures can lead to the evolution of common biological solutions in different groups of organisms (1,12,44).

Radiation resistance is also important in pharmaceutical microbiology because ionizing radiation and UV treatments are widely used in sterilization processes (3). However, the ability of some microorganisms to tolerate these treatments highlights the need to understand the mechanisms underlying radiation resistance (12). Studies on tardigrades and radiation-resistant microorganisms indicate that stress tolerance depends less on the complete prevention of damage and more on the efficient management and repair of damage once it occurs (6,12,18). Preservation of genome integrity, limitation of oxidative damage, and the reactivation of cellular functions following stress are common features of both systems (6,10,12). Evaluating the similar stress responses that occur during dehydration may further improve our understanding of these adaptive mechanisms.

3.3. Microbiological Effects of Dehydration

Water is one of the fundamental requirements for maintaining cellular metabolism. Therefore, a reduction in environmental water availability can lead to important biological consequences, including slower enzymatic reactions, disruption of membrane organization, structural changes in proteins, and disturbances in cellular homeostasis. Depending on the severity and duration of the stress, these effects may be reversible or may ultimately result in cell death (1,2).

Microorganisms have developed various adaptation mechanisms to reduce the effects of desiccation stress (10,45). The synthesis or uptake of compatible solutes is one of the main strategies that help maintain intracellular water balance.

Molecules such as trehalose, proline, glycine betaine, and ectoine not only support osmotic balance but also contribute to protein and membrane stability (2,45). In addition, antioxidant defense systems and DNA repair mechanisms are activated in response to the increased oxidative burden that accompanies dehydration (6,10,18).

There are important functional similarities between the anhydrobiotic response observed in tardigrades and microbial tolerance to dehydration. In both cases, the primary goal is to preserve cellular structures during desiccation and maintain the capacity to resume metabolic activity when favorable conditions return (2,4,11). However, tardigrades exhibit a more complex resilience network because they possess additional protective systems, including tardigrade-specific proteins (7,8).

Dehydration tolerance is of particular importance in pharmaceutical microbiology, especially in the production of probiotics, microbial biopreparations, and live vaccines. Maintaining viability during drying and lyophilization processes directly affects product efficacy. Therefore, understanding natural desiccation-tolerance mechanisms may contribute to the development of more resilient formulations (14).

The effects of dehydration are not limited to individual cells. Many microorganisms become more resistant to environmental stress through biofilm formation and other community-based behaviors under stressful conditions. When considered together with the protective adaptations observed in tardigrades, these responses suggest that stress tolerance in different organisms is based on common biological principles (3,11).

3.4. Similarities to Microbial Resistance Mechanisms

Collectively, the stress responses observed in tardigrades and microorganisms are based on common biological principles,

including the preservation of cellular integrity, metabolic suppression, limitation of oxidative damage, and maintenance of genome stability under adverse conditions. Although the molecular mechanisms involved may differ, strategies such as dormancy, macromolecular protection, antioxidant defenses, and DNA repair serve similar functions in promoting survival and recovery following environmental stress. These shared principles provide valuable insights for the stabilization of biological materials and the development of biomimetic protection technologies (6,10,11,14).

4. ADAPTATION OF TARDIGRADE MECHANISMS TO PHARMACEUTICAL SYSTEMS

The significance of research on tardigrades extends beyond explaining their extraordinary resilience mechanisms. Findings from recent years suggest that the protective systems identified in tardigrades may have practical applications in the development of biological products. Considering the negative effects of environmental factors such as dehydration, temperature fluctuations, and oxidative stress on biological products, interest in new stabilization strategies inspired by natural systems has steadily increased (7,11,14).

Protein-based therapeutics, vaccines, enzyme preparations, and other biological products can be exposed to various environmental stresses during production, storage, and transportation, resulting in a loss of activity. Therefore, preserving biological function is considered one of the primary goals of modern pharmaceutical technology (7,14,48). The protective mechanisms identified in tardigrades provide an important biomimetic model for developing new solutions in this field (7,14,47). Central to these approaches are molecular systems

that enable cellular components to maintain their functions even under low-water conditions (7,19). In particular, the demonstration that tardigrade-specific proteins can protect biological materials from desiccation and other environmental stresses has opened new possibilities for improving the resilience of biological products (7,14).

Many biological products require controlled storage conditions and a continuous cold chain to maintain their efficacy. Mimicking the natural protective systems found in tardigrades may contribute to the development of formulations that remain stable under a broader range of environmental conditions and may offer alternative approaches that reduce dependence on cold-chain storage (7,14,49).

Knowledge gained from tardigrade biology also has potential applications in the development of microbial preparations such as probiotics and live biotherapeutic products. Reducing the loss of viability during production, drying, and storage is critical for maintaining the effectiveness of these products. Therefore, protective strategies inspired by tardigrades may contribute to the development of more resilient biological preparations (7,14). In addition, tardigrade-based biomimetic approaches offer new opportunities for nanocarrier systems, controlled-release platforms, and dermopharmaceutical formulations. Protecting active compounds from environmental stress and improving product stability are among the main goals of research in this area (14,47).

Overall, protective systems inspired by tardigrades hold significant potential for the stabilization of biological products, the preservation of living systems, and the development of next-generation pharmaceutical technologies. However, translating these approaches into clinical and industrial applications will require comprehensive evaluation in terms of efficacy, safety,

manufacturability, and regulatory requirements (7,14). Furthermore, the application of biological systems that enhance stress tolerance also raises important biosafety and ethical considerations that must be carefully addressed.

5. BIOSAFETY, DUAL-USE CONSIDERATIONS, AND FUTURE PERSPECTIVES

The protective mechanisms identified in tardigrades offer important opportunities for the stabilization of biological products and the development of new pharmaceutical technologies. At the same time, the transfer of biological systems that enhance environmental stress tolerance to other organisms or their use in biotechnological applications raises biosafety concerns that require careful consideration. Advances in biotechnology, synthetic biology, and genetic engineering have made it possible to redesign biological systems while also increasing discussions about the dual-use nature of these technologies (15,20,51).

Dual-use research refers to the potential for scientific knowledge or technologies developed for beneficial and peaceful purposes to be used in other ways. The DNA protection systems and stress-tolerance proteins identified in tardigrades provide important opportunities for preserving biological materials and developing more resilient biological systems (6,7,14). However, the theoretical possibility that these mechanisms could be used to create microorganisms with increased resistance to environmental stress should be evaluated within risk-based frameworks (15,20,50). Current evidence indicates that the mechanisms identified in tardigrades do not provide unlimited resilience on their own and that stress tolerance is a complex trait resulting from the combined effects of multiple genetic, physiological, and environmental factors (1,18).

Research on tardigrades has provided valuable insights into the molecular basis of environmental stress tolerance and has established an important scientific foundation for developing new technologies aimed at preserving biological systems (11,14). In particular, findings related to protective proteins and macromolecular stabilization mechanisms have made tardigrade biology an important model not only for basic science but also for biotechnology and pharmaceutical sciences. Future studies are expected to focus on translating the protective systems identified in tardigrades into biomimetic and recombinant approaches for the stabilization of biological products, the preservation of living cells, and the development of formulations with improved resistance to environmental stress (7,14,19,46). However, the widespread application of these technologies will require a comprehensive evaluation of efficacy, safety, biosafety, and regulatory requirements (15,20,46,52).

6. CONCLUSION

Tardigrades represent unique models for understanding environmental stress biology because their resilience depends on the coordinated action of cryptobiosis, macromolecular stabilization, antioxidant defenses, and genome protection systems. The functional similarities between these mechanisms and microbial stress responses provide valuable insights into the preservation of biological materials and the development of biomimetic stabilization strategies. Consequently, tardigrade biology has emerged as an interdisciplinary research field with considerable relevance to pharmaceutical microbiology and biotechnology. Future studies are expected to contribute to the development of next-generation stabilization technologies and more resilient biological products while ensuring that biosafety,

ethical principles, and regulatory considerations remain integral components of translational applications.

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