

CYPRUS

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Clinical Findings on the Relationship Between COVID-19 and Stroke

Erkan Boğa

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Dear Editor,

I have carefully read the article titled “stroke in patients with active coronavirus-2019 (COVID-19) infection: case series in a single center” published in the 2024 issue of the Cyprus Journal of Medical Sciences. Neurological complications of severe acute respiratory syndrome coronavirus-2 infection, particularly its impact on stroke, have been intensively studied since the beginning of the pandemic.¹ This article provides valuable insights into how COVID-19 increases the risk of stroke through mechanisms such as hypercoagulation, endothelial damage, and cytokine storm. The findings of this study clearly highlight the need to evaluate stroke management and preventive measures against COVID-19 in an integrated manner.

The vascular effects of COVID-19, including hypercoagulation and endothelial damage, play a significant role in the pathogenesis of stroke.² Factors such as cytokine storms and elevated D-dimer levels during infection are identified as contributors to thrombus formation.³ A more detailed examination of these mechanisms could enhance our understanding of the systemic effects of COVID-19. The study reported ischemic stroke in 81.8% of the patients and hemorrhagic transformation in 6.1%. Comorbidities such as hypertension, diabetes, and previous stroke were identified as factors exacerbating the severity of stroke in COVID-19 patients. The average age of the cohort underscores the role of aging and coexisting conditions in increasing the disease's impact.

One of the most striking findings of the article is the significantly lower intensive care unit (ICU) admission and mortality rates among vaccinated patients compared to unvaccinated ones. These results demonstrate that COVID-19 vaccines not only prevent infections but also reduce the severity of strokes. Additionally, the study examines the impact of lung involvement on the severity of strokes. Patients with bilateral diffuse ground-glass opacities required ICU care in all cases; their mortality

rates were higher. This finding suggests that COVID-19's systemic effects are not limited to neurological complications but are also associated with pulmonary involvement. Further research is needed to explore the connection between lung involvement and stroke.

While the study provides valuable insights into the relationship between COVID-19 and stroke, the retrospective design limits its generalizability. Larger-scale, multicenter, and prospective studies could further validate these findings. Highlighting the protective effect of vaccination is crucial for preventing complications related to COVID-19. Moreover, increasing research on long-term outcomes of stroke after COVID-19 could address existing knowledge gaps in this area.

In conclusion, this article significantly contributes to raising awareness about the management of COVID-19 and stroke while offering valuable insights for clinical practices.

Footnotes

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Challenges of Cerebral Hemodynamic Disorders and Hypoxic-Ischemic Encephalopathy: Evaluating Current and Emerging Approaches from Neurological Emergencies to Intensive Care

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Abstract

Cerebral hemodynamic disorders and hypoxic-ischemic encephalopathy (HIE) pose significant challenges across various stages of medical care, from neurological emergencies to intensive care. These conditions, marked by impaired cerebral perfusion and oxygenation, lead to severe neurological deficits and present a complex interplay of pathophysiological mechanisms. This review provides a comprehensive evaluation of both current and emerging approaches to managing these disorders. It examines the pathophysiology of cerebral hemodynamic disturbances and HIE, focusing on the critical role of cerebral blood flow and oxygen delivery in brain function. The paper reviews existing diagnostic tools, including neuroimaging and biomarkers, and their limitations in detecting and assessing the severity of these conditions. It also highlights advances in therapeutic strategies, such as neuroprotective agents, advanced monitoring techniques, and novel interventions, aimed at improving patient outcomes. Special emphasis is placed on the transition from acute management in neurological emergencies to ongoing care in intensive settings, addressing the need for a multidisciplinary approach and continuous innovation. By integrating recent research findings and clinical experiences, this review underscores the importance of addressing these challenges to enhance patient care and optimize treatment outcomes for cerebral hemodynamic disorders and HIE.

Keywords: Cerebral blood flow, cerebral hemodynamics, hypoxic-ischemic encephalopathy, imaging methods, treatments

INTRODUCTION

Cerebral hypoperfusion is a critical condition characterized by inadequate blood flow to the brain, which can lead to significant neurological impairments and, if persistent, irreversible brain damage.¹ Due to the brain's high metabolic demands and limited energy reserves, it is especially vulnerable to reductions in blood supply.² Understanding the mechanisms, clinical implications, and management strategies of cerebral hypoperfusion is crucial for improving patient outcomes across various acute and chronic conditions.³ Research and clinical practices are continually evolving to address these complexities and advance

therapeutic approaches that mitigate neurovascular compromise and promote neurological recovery.

The recent review explores the multifaceted interplay between blood gas alterations and cerebral hypoperfusion, highlighting their profound impact on neurological function and clinical outcomes.

Mechanisms of Hypoxic-Ischemic Encephalopathy

Hypoxic-ischemic encephalopathy (HIE) is a severe brain injury resulting from a critical reduction in cerebral blood flow (CBF) and oxygen supply, leading to a cascade of pathological events that compromise

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neuronal function and viability.⁴ The initial insult is characterized by hypoxia and ischemia, which disrupt cellular metabolism and deplete adenosine triphosphate (ATP) reserves, impairing the function of ATP-dependent ion pumps. This failure leads to neuronal depolarization and the accumulation of intracellular calcium and sodium, triggering excitotoxicity mediated by excessive glutamate release. Subsequently, the influx of calcium activates various enzymes, such as proteases, phospholipases, and endonucleases, which damage cellular structures, including membranes, cytoskeleton, and DNA.⁵ Additionally, the overproduction of reactive oxygen species (ROS) and nitric oxide during the reoxygenation phase exacerbates oxidative stress, further harming neuronal and glial cells. The ensuing inflammatory response, characterized by the activation of microglia and the infiltration of leukocytes, releases cytokines and chemokines that perpetuate tissue damage.⁶ The combination of excitotoxicity, oxidative stress, and inflammation ultimately leads to apoptosis and necrosis of neural cells, resulting in the characteristic neurological impairments associated with HIE.⁷ Understanding these mechanisms is crucial for developing targeted therapeutic interventions aimed at mitigating neuronal damage and improving clinical outcomes in affected individuals.

Causes of Hypoxic-Ischemic Encephalopathy

Systemic causes of cerebral hypoperfusion: Cerebral hypoperfusion can arise from various systemic factors that compromise cerebral perfusion pressure (CPP).⁸ One of the primary systemic causes is systemic hypotension, where a significant drop in mean arterial pressure results in reduced CPP, leading to decreased CBF.⁹ Conditions such as shock, severe dehydration, or hemorrhage can precipitate systemic hypotension, further complicating cerebral perfusion. Impaired cardiac output, due to cardiac conditions like myocardial infarction, heart failure, or arrhythmias, also plays a critical role in cerebral hypoperfusion.¹⁰ These conditions reduce the heart's ability to pump sufficient blood to the brain, thereby impairing oxygen and nutrient delivery to neural tissues. Cardiac arrest, in particular, causes an abrupt cessation of CBF, leading to global cerebral ischemia and potential neurological damage.¹¹ Additionally, the inappropriate use or overuse of antihypertensive medications, sedatives, and anesthetics can induce systemic hypotension, contributing to decreased cerebral perfusion.¹²

Local vascular causes of cerebral hypoperfusion: Local vascular factors are significant contributors to cerebral hypoperfusion, often leading to focal reductions in blood flow to specific brain regions. Obstruction of major cerebral arteries, commonly due to embolism or thrombosis, is a primary cause of localized cerebral hypoperfusion.¹³ Conditions such as ischemic stroke and transient ischemic attacks result from these obstructions, which reduce blood supply to affected brain regions and cause neurological deficits. Severe atherosclerosis, characterized by the buildup of plaques within the arterial walls, can also lead to reduced CBF by narrowing the arteries and restricting blood passage.¹⁴ Vasculitis, an inflammatory condition affecting blood vessels, can further contribute to vessel narrowing and occlusion, exacerbating the risk of cerebral hypoperfusion.¹⁵ Furthermore, small vessel disease, particularly prevalent in individuals with diabetes, leads to endothelial dysfunction and damage to the microvasculature within the brain, significantly impacting cerebral perfusion. The compromised integrity of small blood vessels results in chronic cerebral hypoperfusion and poses a risk for cognitive decline and neurodegenerative conditions.¹⁶

Age-related and neurological factors in cerebral hypoperfusion: Age-related changes in the cardiovascular and neurological systems also play a critical role in the development of cerebral hypoperfusion. As individuals age, structural and functional changes in the cardiovascular system, such as increased arterial stiffness and reduced cardiac output, can diminish CBF.¹⁷ These changes lead to a decrease in the brain's ability to maintain adequate perfusion, contributing to the risk of cerebral hypoperfusion in the elderly. Orthostatic hypotension, a condition more prevalent in older adults, causes transient reductions in CBF upon standing, increasing the risk of dizziness, falls, and syncope.¹⁸ Additionally, neurological conditions can impair the brain's autoregulatory mechanisms, increasing intracranial pressure (ICP) and reducing CPP.⁹ The inability of cerebral vessels to adequately regulate blood flow in response to changes in systemic blood pressure can exacerbate the risk of hypoperfusion, leading to potential neurological damage.¹⁹ Understanding these age-related and neurological factors is essential for developing targeted interventions to mitigate cerebral hypoperfusion and its associated risks.

Clinical Manifestations

Cerebral hypoperfusion can lead to a range of clinical manifestations depending on the severity, duration, and areas of the brain affected. These manifestations can be acute or chronic and may vary from transient mild symptoms to severe and lasting neurological deficits.²⁰

Acutely, one of the primary manifestations is syncope, characterized by a sudden and temporary loss of consciousness. This condition often results from a significant, albeit brief, reduction in CBF, which can occur in orthostatic hypotension or episodes of severe systemic hypotension.²¹ Another acute manifestation is cognitive impairment, presenting as acute confusion or delirium. This condition is marked by disorientation, an inability to concentrate, and fluctuating levels of awareness, attributable to transient cerebral hypoperfusion. Short-term memory loss is also common in such scenarios where patients fail to recall recent events due to compromised blood flow in the vertebrobasilar artery system.²²

Furthermore, focal neurological deficits, sensory changes, dizziness, and vertigo, visual or speech disturbance, closely mimicking stroke symptoms, are frequently observed in acute cases of inadequate cerebral perfusion.²³

In contrast, chronic manifestations of inadequate CBF are characterized by more persistent and progressive conditions. Cognitive decline is a major concern, with vascular dementia being a prominent outcome. This condition involves a gradual deterioration in cognitive function, marked by memory impairment, executive dysfunction, and difficulties with reasoning and planning, often due to chronic cerebral hypoperfusion leading to small vessel disease.²⁴ Subcortical ischemic vascular disease, associated with white matter lesions and lacunar infarcts, is another chronic cognitive impairment linked to sustained hypoperfusion.²⁵ Chronic cerebral hypoperfusion can also lead to psychiatric symptoms, including depression and anxiety, as it impacts brain regions involved in mood regulation, such as the amygdala.²⁶

Motor dysfunction is another significant chronic manifestation. Patients may develop gait disturbances, characterized by impaired coordination and walking difficulties often described as a "shuffling gait." This is due to chronic hypoperfusion affecting the basal ganglia and white matter tracts. Parkinsonism, exhibiting symptoms such as bradykinesia, rigidity,

and tremors, can also develop over time with prolonged inadequate blood flow to extrapyramidal motor control regions.²⁷

Overall, these acute and chronic manifestations highlight the extensive and varied impact that inadequate CBF can have on different bodily systems and functions, necessitating timely and effective medical interventions to mitigate these effects.

Diagnosis and Monitoring

Clinical examination: Early diagnosis of cerebral hypoperfusion is critical for timely intervention and management. Key diagnostic tools encompass a multidimensional approach aimed at promptly identifying underlying causes and assessing the extent of CBF compromise.

The clinical examination of patients with HIE is a critical component of the diagnostic process, offering essential insights into the severity of cerebral injury and guiding immediate and long-term management strategies. Upon initial assessment, the evaluation typically begins with the determination of the patient's level of consciousness using the Glasgow Coma Scale (GCS), which quantitatively measures eye, verbal, and motor responses.²⁸ A lower GCS score, particularly a score of 8 or less, is indicative of severe neurological impairment and necessitates prompt intervention.²⁹ In addition to GCS, the examination of brainstem reflexes, including pupillary light reflexes, corneal reflexes, and oculocephalic responses, provides important information about brainstem integrity. Absent or asymmetric pupillary reactions, for instance, may suggest extensive brainstem or midbrain damage due to hypoxia.³⁰

Motor responses are closely evaluated for the presence of decerebrate or decorticate posturing, both of which are associated with significant brain injury. Decerebrate posturing, characterized by extension and internal rotation of the arms and legs, typically indicates damage to the brainstem, while decorticate posturing, with flexion of the upper limbs and extension of the lower limbs, suggests injury above the level of the red nucleus, such as in the thalamus or cerebral hemispheres.³¹ In the acute phase, myoclonus, a form of involuntary muscle jerking, may also be observed and is often associated with poor prognosis.³²

Cranial nerve examination indicates localized brain injury or diffuse hypoxic damage. For instance, the presence of a unilateral cranial nerve deficit, such as facial asymmetry or dysphagia, may point to focal ischemic events secondary to HIE.³³ Furthermore, the presence of spontaneous or reflexive eye movements, or the lack thereof, can provide additional prognostic information; for example, absent oculocephalic reflexes may signify extensive brainstem involvement.³⁴

In addition to neurological findings, a thorough systemic examination is necessary to identify potential underlying causes of hypoxia, such as cardiac arrest, respiratory failure, or severe hypotension, and to assess for signs of systemic hypoperfusion or multiorgan dysfunction.³⁵ Serial clinical examinations are essential, as they allow for the monitoring of neurological status over time, helping to track the progression or resolution of HIE and to adjust therapeutic strategies accordingly. The integration of clinical examination findings with laboratory, neuroimaging, and electrophysiological studies forms the foundation of comprehensive management in HIE, facilitating timely and appropriate interventions aimed at optimizing neurological outcomes.³⁶

Role of blood gas changes on cerebral perfusion: Blood gases, including PaCO_2 , PaO_2 , and pH, play pivotal roles in the regulation of

CBF. Alterations in these parameters can lead to significant changes, impacting brain function and potentially leading to neurological damage.³⁷ Understanding these components and their significance in hypoperfusion helps in diagnosing, managing, and monitoring a wide range of clinical conditions, ensuring optimal care in patients with cerebral hypoperfusion.³⁸

Arterial blood gas analysis (ABGa) provides direct measurements that offer insights into the overall metabolic and respiratory functions. Pulse oximetry allows continuous, non-invasive monitoring of oxygen saturation, which is useful for detecting and managing hypoxemia in real-time. While convenient, pulse oximetry may not always accurately reflect PaO_2 , particularly in cases of poor peripheral perfusion or carbon monoxide poisoning.³⁹

Hypoxemia stabilizes hypoxia-inducible factors (HIFs), which regulate the expression of genes involved in adaptive responses to low oxygen, such as angiogenesis, erythropoiesis, and metabolic shifts.⁴⁰ Kaelin et al.⁴¹ the pioneer researchers in HIFs, have been awarded with the Nobel Prize with the research describing the important key proteins and key enzymes that participate in oxygen sensing and compensating pathways. HIFs have been maintaining their importance as an attractive and feasible target of therapeutic interventions to prevent the irreversible effects of acute or chronic hypoxemia.⁴²

Hypercapnia induces various physiological changes that significantly affect CBF. Carbon dioxide readily diffuses across the blood-brain barrier (BBB) and combines with water to form carbonic acid, which dissociates into hydrogen ions and bicarbonate. The increase in hydrogen ions, acidosis, directly dilates cerebral blood vessels. Hypercapnia-induced acidosis also affects cellular metabolism, shifting the energy production from oxidative phosphorylation to glycolysis, which is less efficient and produces lactic acid. Potassium channels in cerebral blood vessels are activated by hypercapnia, causing hyperpolarization of smooth muscle cells and resulting in vasodilation. Hypercapnia-induced vasodilation can initially enhance cerebral perfusion, potentially beneficial in conditions with compromised CBF.¹⁹ However, excessive or prolonged vasodilation can lead to increased intracranial pressure. Sustained hypercapnia may cause cerebral edema and elevated ICP, which can risk herniation and brainstem compression.³

Lactate has long been recognized as a marker of tissue hypoperfusion and hypoxia.⁴³ During hypoperfusion, oxygen delivery to tissues is insufficient to meet metabolic demands. Cells switch from aerobic to anaerobic metabolism, resulting in increased lactate production. The degree of lactate elevation correlates with the severity of hypoperfusion and can guide therapeutic interventions. Elevated lactate levels in CSF and blood may also reflect underlying mitochondrial dysfunction, not solely hypoxia, providing insights into neuronal health.⁴⁴ Ischemic stroke leads to localized cerebral hypoperfusion, causing rapid lactate accumulation in the affected brain region. Monitoring lactate levels during thrombolytic or endovascular therapy can provide insights into reperfusion success and tissue viability.⁴⁵ During cardiac arrest, the cessation of blood flow leads to global hypoxia and a rapid rise in lactate levels. Elevated lactate levels persist after return of spontaneous circulation (ROSC) due to ongoing tissue hypoxia and reperfusion injury, generally. Lactate levels can be used as a guide to evaluate the effectiveness of resuscitation efforts and the adequacy of oxygen delivery post-ROSC.⁴⁶

Blood gas components interact with each other, and changes in one parameter affect others. For example, respiratory acidosis often prompts renal adjustments in bicarbonate levels, which is crucial for the blood's buffering system, maintaining pH within a narrow range.⁴⁷ Regular ABGa analysis is essential, particularly in intensive care settings for patients on mechanical ventilation or those with respiratory or metabolic disorders. Persistent or severe blood gas disturbances are associated with poor neurological outcomes. Early recognition and correction of these disturbances are crucial for improving patient prognosis and preventing long-term brain damage.

Current and emerging techniques in neuroimaging and diagnostic tools: Neuroimaging plays a role not only in the diagnosis, but also in prognostication and management of HIE in adults by providing critical insights into the extent and distribution of brain injury following a hypoxic event. Among the neuroimaging modalities, magnetic resonance imaging (MRI) is considered the gold standard for evaluating HIE due to its superior sensitivity in detecting both acute and chronic ischemic changes.⁴⁸ Diffusion-weighted imaging (DWI) is particularly valuable in the early detection of cytotoxic edema, which manifests as hyperintense regions on DWI and corresponds to areas of acute neuronal injury. These changes are often observed within hours of the hypoxic insult, with the basal ganglia, thalamus, hippocampus, and watershed areas being particularly vulnerable due to their high metabolic demand.⁴⁹ Fluid-attenuated inversion recovery sequences complement DWI by highlighting subacute and chronic ischemic changes, including gliosis and encephalomalacia, which may develop days to weeks after the initial event.⁵⁰

As an emerging neuroimaging technique, functional MRI assesses brain activity by measuring changes in blood oxygenation, providing insight into the impact of HIE. It is being explored, along with diffusion tensor imaging techniques, for its potential to assess microstructural changes and functional connectivity disruptions in HIE.⁵¹

In addition to conventional MRI sequences, advanced techniques such as magnetic resonance spectroscopy (MRS) and perfusion MRI (pMRI) provide further insights into the metabolic and hemodynamic status of the brain. MRS allows for the non-invasive assessment of brain metabolites, including lactate, N-acetylaspartate (NAA), and choline, which can be altered in the context of ischemia. Elevated lactate levels detected by MRS indicate anaerobic metabolism, a hallmark of hypoxic injury, while reduced NAA levels suggest neuronal loss or dysfunction.⁵² pMRI, on the other hand, enables the quantification of CBF and volume, providing crucial information about the adequacy of cerebral perfusion and identifying areas at risk of further infarction. Regions with significantly reduced perfusion are at higher risk of irreversible damage, guiding decisions regarding potential therapeutic interventions.⁵³

Newer approaches, like arterial spin labeling MRI, a non-contrast method that magnetically labels inflowing blood to measure CBF, are being explored as a safer alternative for detecting early perfusion deficits in HIE patients, especially those with contraindications to contrast agents.⁵⁴

Computed tomography (CT), although less sensitive than MRI, remains an essential tool in the acute setting due to its widespread availability and rapid acquisition. Non-contrast scans can identify early signs of hypoxic brain injury, such as the loss of gray-white matter differentiation, diffuse cerebral edema, and the presence of "reversal sign" or "white

cerebellum sign," which are associated with poor prognosis.⁵⁵ CT perfusion imaging, similar to MRI, provides insights into CBF and can help differentiate between salvageable penumbra and infarcted core in the ischemic brain.⁵³

Electroencephalography (EEG) provides real-time assessment of cerebral function and aids in both diagnosis and prognostication. In the acute phase of HIE, EEG is particularly valuable for detecting subclinical seizures, which are common in the context of diffuse brain injury but may not manifest with overt clinical signs. The presence of seizures on EEG is associated with further neuronal damage and can significantly worsen outcomes if not promptly managed.⁵⁶ In addition to identifying seizures, EEG patterns can reflect the severity of the encephalopathy. For instance, the presence of periodic discharges, burst suppression patterns, or generalized slowing on EEG often correlates with more severe brain injury and poorer neurological outcomes. Burst suppression is characterized by alternating periods of high-amplitude activity and flat line or low-amplitude activity and, in particular, is typically indicative of severe and often irreversible brain damage.⁵⁷

Continuous EEG monitoring is frequently employed in the intensive care setting to provide ongoing evaluation of brain activity in patients with HIE, particularly those undergoing therapeutic interventions such as hypothermia.⁵⁸ This continuous monitoring allows for the timely detection and treatment of seizures and provides valuable information on the evolution of the encephalopathy over time. The reactivity of the EEG, defined as the ability of brain activity to change in response to external stimuli, is another important prognostic indicator. An EEG that lacks reactivity, especially in the absence of sedative medications, is generally associated with a poor prognosis.⁵⁹ Beyond seizure detection, quantitative EEG analysis, which involves the mathematical processing of EEG signals to extract additional information, is increasingly being explored for its potential to provide more nuanced prognostic data.⁶⁰

Evoked potentials (EPs) are valuable electrophysiological tools in the assessment of HIE, offering objective measures of sensory pathway integrity and brainstem function. Among the various types of EPs, somatosensory evoked potentials (SSEPs) and brainstem auditory evoked potentials (BAEPs) are most commonly employed in the context of HIE.⁶¹ The prognostic value of EPs has been well-established, with studies consistently showing that absent cortical responses on SSEPs, particularly the N20 wave, are strongly predictive of poor outcomes in comatose patients following cardiac arrest, a common cause of HIE in adults. Similarly, the presence of prolonged latencies or the absence of key waveforms in BAEPs suggests extensive brainstem injury and is correlated with a higher likelihood of adverse outcomes, including persistent vegetative state or death.⁶²

Biomarkers are emerging as valuable tools in the diagnosis, prognostication, and management of HIE in adults, offering the potential to detect brain injury at the molecular level and predict outcomes with greater accuracy. Among the most studied biomarkers in HIE are neuron-specific enolase (NSE), S100B protein, and glial fibrillary acidic protein (GFAP).⁶³ NSE is often elevated in correlation with the extent of brain damage and poor neurological outcomes in HIE patients. Measuring NSE levels in serum within the first 24 to 48 hours post-injury offers valuable prognostic information, aiding in the identification of patients who may benefit from aggressive neuroprotective therapies.⁶⁴

S100B protein, primarily expressed by astrocytes, serves as a biomarker for glial cell damage and BBB disruption. Elevated serum S100B levels are associated with the severity of brain injury in HIE, with higher concentrations predicting a higher risk of death or severe neurological impairment; and its combination with other biomarkers or clinical parameters improves long-term prognostic accuracy.⁶⁵

GFAP, an intermediate filament protein specific to astrocytes, is released into the bloodstream following astroglial injury and has emerged as a promising early biomarker for brain injury in HIE. Its elevated levels are useful in distinguishing between traumatic and non-traumatic brain injuries and in assessing the severity of diffuse axonal injury. Studies show that high GFAP levels within hours of the hypoxic event strongly predict poor neurological outcomes, highlighting its clinical utility.⁶⁶

In addition to these established biomarkers, ongoing research is exploring the role of other molecules, such as microRNAs, interleukins, and oxidative stress markers, in the pathophysiology of HIE.⁶⁷ These novel biomarkers may provide further insights into the mechanisms of brain injury and recovery, potentially leading to the development of targeted therapeutic strategies. The integration of biomarker analysis with other diagnostic modalities, such as neuroimaging and electrophysiological studies, offers a more comprehensive approach to the management of HIE, enabling personalized treatment plans that are tailored to the specific needs of each patient.

Cerebral oximetry, a non-invasive technique using near-infrared spectroscopy to measure regional cerebral oxygen saturation, is becoming increasingly important in managing HIE in adults. It offers a real-time assessment of cerebral oxygenation, directly monitoring brain tissue oxygenation, unlike traditional systemic measures.⁶⁸ During therapeutic hypothermia, cerebral oximetry helps maintain safe oxygenation levels, reducing the risk of hypoxic episodes or reperfusion injury.⁶⁹ However, it mainly measures cortical oxygenation and can be influenced by factors like scalp edema and sensor placement, requiring careful interpretation. As technology advances, cerebral oximetry is expected to play an even greater role in neurocritical care, despite its current limitations.⁷⁰ Additionally, cerebral oximetry can be integrated with other monitoring modalities, such as EEG and ICP monitoring, to provide a comprehensive assessment of cerebral function and guide tailored interventions.⁷¹ Despite these challenges, as technology advances and more research is conducted, the role of cerebral oximetry in HIE is likely to expand, further solidifying its place in neurocritical care.

Current and Emerging Treatments

In adults, the management of HIE focuses on limiting brain injury and promoting recovery through various pharmacological and neuroprotective strategies. One of the primary treatments under investigation is therapeutic hypothermia, which has shown success in neonates and is being explored for adult patients.⁷² This approach involves cooling the body to reduce metabolic demand and inflammation, thereby mitigating brain damage.⁵⁸ Additionally, antioxidants such as N-acetylcysteine and edaravone are studied for their potential to reduce oxidative stress, a critical factor in neuronal injury following ischemic events.⁷³

Anti-inflammatory drugs also play a significant role in HIE management. Minocycline, for instance, has demonstrated promise

in reducing microglial activation and inflammation, which are key contributors to secondary brain injury.⁴ Another critical area of focus is the prevention of glutamate excitotoxicity, a process in which excessive glutamate causes neuronal death. N-methyl-D-aspartate receptor antagonists like memantine are being investigated for their ability to counteract this mechanism. Similarly, calcium channel blockers such as nimodipine, traditionally used to manage subarachnoid hemorrhage, are considered for their potential to reduce calcium-mediated neuronal injury in HIE.⁷⁴

In terms of neuroprotective strategies, erythropoietin has emerged as a potential therapeutic agent due to its anti-apoptotic and anti-inflammatory properties, which extend beyond its role in stimulating red blood cell production.⁴ Stem cell therapy is another promising approach, with mesenchymal stem cells and neural stem cells showing potential in repairing and regenerating damaged brain tissue, although this field remains largely experimental. Growth factors, including insulin-like growth factor 1 and brain-derived neurotrophic factor, are also being explored for their roles in enhancing neuronal survival and promoting regeneration.⁷⁵

Emerging therapies such as exosome-based treatments and preconditioning strategies are gaining attention in the scientific community. Exosomes, which are small vesicles that carry proteins, lipids, and RNAs, are being researched for their ability to deliver neuroprotective agents to the brain. Ischemic preconditioning, where brief episodes of sub-lethal ischemia are induced to build resistance to more severe ischemic insults, represents another innovative approach under investigation.⁶⁷ Furthermore, gene therapy offers a cutting-edge strategy by potentially enhancing the expression of protective genes or suppressing harmful ones in the context of HIE.⁷⁶

The integration of combination therapies is a growing area of interest, as combining different pharmacological agents with neuroprotective strategies may yield better outcomes for patients. Although many of these strategies are still in experimental stages, they represent the future of HIE management, aiming to improve neurological recovery and reduce long-term disabilities associated with this condition.

CONCLUSION

Cerebral hypoperfusion is a critical condition with far-reaching implications for brain health. Effective management of cerebral hypoperfusion requires a comprehensive, multidisciplinary approach that addresses both acute and long-term needs. Early diagnosis and prompt intervention are critical to minimizing neuronal damage and improving outcomes. Advances in imaging techniques, neuroprotective therapies, and personalized medicine hold promise for enhancing the management of cerebral hypoperfusion in the future. Ongoing research is needed to better understand the pathophysiology of cerebral hypoperfusion, identify novel biomarkers, and develop targeted therapies. Integrating emerging technologies such as artificial intelligence and machine learning into clinical practice may improve the accuracy of diagnosis and the precision of treatment strategies.

MAIN POINTS

- Due to the brain's high metabolic demands, cerebral hypoperfusion rapidly leads to irreversible neurological damage, and chronic hypoperfusion contributes to vascular dementia and motor dysfunction, resulting in long-term complications.

- Disruptions in cerebral perfusion set the stage for progressive neurological deterioration, bridging acute deficits with chronic neurodegeneration.
- Multimodal neurodiagnostics, including advanced imaging techniques and electrophysiological assessments, alongside emerging biomarkers, provide a comprehensive framework for detecting hypoxic brain injury, prognosticating outcomes, and guiding therapeutic interventions.
- Neuroprotective interventions, ranging from therapeutic hypothermia and anti-inflammatory strategies to emerging stem cell and genetic therapies, hold transformative potential in mitigating neuronal injury and enhancing long-term recovery in hypoxic-ischemic encephalopathy.

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A Review of the Anti-Breast Cancer Activity of Non-Endemic Medicinal Plants in Cyprus

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Abstract

Breast cancer is a widespread health concern that begins in the breast cells and leads to uncontrollable growth of these cells. This disease has a physiological basis as it is associated with physical abnormalities arising from defective genes in breast cancer genes, such as *BRCA1* and *BRCA2*, and non-functional tumor suppressor genes, such as *p53*, which leads to the transformation of tissues into malignant and metastatic forms. Despite the progressive modern methods of cancer treatment with the help of chemotherapy, radiation therapy, surgery, endocrine therapy, and immunotherapy, most treatments result in furious side effects that disturb patients' quality of life. As a result, researchers and scientists have shifted their focus to medicinal plants and their secondary metabolites as potential treatments for breast cancer. This research aims to review the medicinal plants used in Cyprus for lethal diseases, such as breast cancer, from various species of herbs, as well as the knowledge generated from traditional practices and recent studies. This study also describes the geographical origins, status, and potential applications of these plants in breast cancer treatment, providing valuable insights into their therapeutic value.

Keywords: Breast cancer, bioactive compounds, complementary therapy, medicinal plants

INTRODUCTION

Globally, breast cancer has emerged as a significant cancer, with >2.3 million diagnoses and 685,000 deaths reported in 2020 alone.¹ Equivalent to these results, based only on Cyprus, as seen in studies conducted between 2004 and 2017, the rate of breast cancer per 100,000 people, especially in the elderly population, increased from 135.3 to 153.2.² Breast cancer is a disease that affects most people and has a significant impact worldwide. It is caused by the mutation of breast cells and their uncontrolled growth and spread.³ Physiologically, breast cancer occurs when specific genes of breast cells become defective, resulting in uncontrollable growth of cell clusters.⁴ Changes in

genes like *BRCA1* and *BRCA2*, which repair DNA and direct cell division, can accompany this process.⁵ Thereby, the loss of function in tumor suppressor genes such as *p53* and disruption of cell cycle regulators also leads to malignant transformation of cells.⁶ Furthermore, new blood vessel formation (angiogenesis) sustains tumor growth potentials for metastasis, which is the spread of cancer cells to other regions of the body.⁷ Modern medicine's oncological developments in breast cancer treatment are driving efforts to alter the disease's trajectory through combined or simple treatment methods.⁸ These treatment methods are associated with cell cycle regulation and apoptosis stimulation, and they include the stimulation of the supporting immune system stimulation.^{9,10} Comprehensive modern medical applications carried

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out to examine these effects in oncology include treatment methods such as chemotherapy, radiotherapy, surgical intervention, hormone therapy, and immunotherapy, and the application to be used is decided according to the course of treatment and the stage and type of breast cancer.^{11,12} Despite the significant advancements in medicine, these treatment methods still cause side effects, such as nausea, vomiting, decreased immunity, and fatigue, which can significantly lower the patient's quality of life.¹³ Therefore, researchers are focusing on secondary metabolites found in plants to enhance patients' overall quality of life and prevent damage to healthy tissues that conventional methods may cause.¹⁴ Secondary metabolites are organic compounds produced by medicinal plants but are not directly involved in their growth, development, or reproduction.¹⁵ When used in cancer cells, secondary metabolites exhibit anticancer activity. These substances can prevent cancer cell overgrowth, trigger apoptosis, or inhibit cell proliferation.¹⁶ Therefore, medicinal plants and their secondary metabolites can be considered a safer treatment strategy for breast cancer.¹⁷ In the field of cancer treatment using medicinal plants in Cyprus, this approach has an intriguing aspect due to the rich herbal biodiversity and herbal medicine knowledge provided by the Mediterranean climate.¹⁸

The purpose of this narrative review is to gather research on how local medicinal herbs in Cyprus can protect against breast cancer. The local populace in Cyprus places historical and contemporary value on the plants chosen for this study. This review marks a significant milestone as it delves into the anti-cancer capabilities of medicinal plants that grow wild in Cyprus. The results are summarized in Table 1. For this investigation, we identified pertinent plants by consulting the most recent sources. The medicinal plants reviewed are *Aloe Vera*, *Artemisia Annua*, *Calendula Officinalis*, *Catharanthus Roseus*, *Ceratonia Siliqua*, *Cicer Arietinum*, *Citrullus Colocynthis*, *Ficus Carica*, *Glycyrrhiza Glabra*, *Hordeum Vulgare*, *Myrtus Communis*, *Nigella Sativa*, *Olea Europaea*, *Rosmarinus Officinalis*, and *Silybum Marianum*. According to the evaluated sources, some of these plants are indigenous (IN) to Cyprus, while others are considered casual (CA). While plants classified as casual have not yet established a stable habitat and may not stay there permanently, those classified as IN naturally thrive and adapt to certain geographic locations or ecosystems.¹⁹

Method

A narrative overview of the literature was conducted using Google Scholar, PubMed, and Web of Science. The database was searched using relevant keywords, including MCF-7 cells, anticancer properties, medicinal plants, breast cancer, MDA-MB-231, and MDA-MB-436. To obtain recent findings, scientific articles published in 2018 and later were selected. The most common plants that have traditional uses in Cyprus and are easily accessible by local people were selected and included in this study. This study summarizes the anti-breast cancer activity of plants that are globally accessible, excluding endemic species found only in Cyprus. By focusing on widely distributed plants, this study highlights those with broader availability. The "Flora of Cyprus" website has also been utilized to offer details regarding the status and distribution of medicinal plants in Cyprus. According to this dynamic checklist, the island is divided into eight phytogeographic regions, which are listed from division 1 to division 8, as shown in Figure 1. The different ecological characteristics define each region. Division 1 is the Akamas Peninsula; division 2 is the Troodos Range; division 3 is the South Area around Limassol; division 4 is the Larnaca Area; division 5

is the East part of the Central Plain; division 6 is the West part of the central plain; division 7 is the North Slopes and Peaks of Pentadactylos; and division 8 is the Karpasia Peninsula.²⁰

Medicinal Plants with Antibacterial Activity Against Breast Cancer

Aloe vera

Aloe vera, also known as *Aloe barbadensis* Mill., belongs to the Asphodelaceae family. It is named after the Arabic word "Alloeh," referring to "shining bitter substance," and the Latin word "vera," which refers to "true." *Aloe vera* was esteemed as "the plant of immortality" by the ancient Egyptians. It boasts triangular, succulent leaves with jagged edges, golden tubular blooms, and fruit carrying numerous seeds.^{21,22} Traditionally, *Aloe vera* resin has been used to treat ailments like diabetes, obesity, and various types of infections.²³ Its historical uses span constipation relief, wound healing, and notably, the combat against tumors, which is also acknowledged in Chinese materia medica.^{22,23} *Aloe vera*, which has many uses in tradition, is used daily by local people in Cyprus, mostly by applying the liquid inside the leaf to heal burns.²⁴ In addition, this resilient succulent appears to be CA in the island's botanical realm. Divisions 1, 4, and 6 indicate specific geographically defined regions where the resilient succulent thrives (Figure 2).²⁵ Studies investigating the anti-cancer activity of *Aloe vera* compounds against breast cancer cell lines. Aloe-emodin and ALE- α -Fe2O3NPs obtained from *Aloe vera* leaf extract appear to be effective anticancer agents against MCF-7 cells by inducing apoptosis via mitochondrial and endoplasmic reticulum pathways while inhibiting metastatic oxidative stress by itself.^{21,26} Furthermore, studies have shown that aloe-emodin, 7-hydroxy-2,5 dimethylchromene, and betasitosterol compounds have a higher binding affinity toward estrogen alpha receptor when compared to tamoxifen.²⁷ Moreover, researchers found barbaloin, aloe-emodin, aloesin, and aloin to be cytotoxic compounds active against MCF-7 and MDA-MB-231 breast cancer cell lines. They act by inhibiting cell proliferation and inducing cell death.²⁸ In addition, 7-demethylsiderin, which was extracted from *Aloe vera* resin, had the strongest cytotoxic effect on MDA-MB-231 breast cancer cells.²³

Artemisia annua

Botanists often refer to *Artemisia annua*, also known as sweet Wormwood, as the largest species in the genus *Artemisia annua*, belonging to the Asteraceae family. The name of this life form clearly indicates that it is an annual herbaceous plant, which means it grows annually. It follows the annual breeding process. *Artemisia annua* has versatile anatomical and morphological attributes. Its stems appear either bare or adorned with T-shaped hairs, while the upper layers house glandular cells that are rich in essential oil. The tiny, spherical form and yellow-green coloration of the flower heads, which are arranged in raceme-like inflorescences, distinguish them. Although the leaves emit a pleasant aroma, the flowers have no odor.²⁹ Historically, people have used *Artemisia annua* in various forms, like tea or pressed juice, to treat malaria, fever, and neurological disorders.²⁹⁻³² The *Artemisia annua* is commonly consumed among the people of Cyprus, often through the consumption of infusion tea derived from its flowers and young leaves. It is known for its ability to suppress cough and regulate menstruation. Furthermore, studies have shown that its flowers possess additional pharmacological properties, such as aphrodisiac, antipyretic, and antispasmodic effects.²⁴

Table 1. Summary of the anti-breast cancer activities of medicinal plant extracts and their isolated bioactive compounds

Plant	Bioactive compounds and their mechanism of action	Cell lines	Divisions	References
<i>Aloe vera</i>	Compounds from aloe vera, including aloe-emodin, ALE- α -Fe ₃ O ₃ NPs, barbaloin, aloin, and 7-demethylsiderin, exert anticancer effects by promoting apoptosis and suppressing cell growth in breast cancer cells. The chemicals induce apoptosis through mitochondrial and endoplasmic reticulum stress pathways, mitigate metastatic oxidative stress, and interact with estrogen receptors. 7-demethylsiderin specifically targets carbonic anhydrase II.	MCF-7, DA-MB-231	1, 4, 6	21,23,26-28
<i>Artemisia annua</i> (Wormwood)	It exhibits potent anticancer capabilities via its bioactive components, promoting apoptosis and cell cycle arrest in neoplastic cells. Compounds such as chrysosplenol D, cacticin, and dihydroartemisinin are responsible for these effects. The plant's chemicals promote apoptosis, induce cell cycle arrest at both G1 and G2/M stages, and suppress tumor growth by targeting proteins such as CD44, Oct 3/4, and MMP-9. Dihydroartemisinin augments the efficacy of chemotherapy (docetaxel), whereas artesunate causes both ROS-dependent and ROS-independent cell cycle arrest.	MDA-MB-231, MCF-7	6	9,16,24,25,29-32
<i>Calendula officinalis</i> (Marigold)	The extracts exhibit specific cytotoxicity toward cancer cells while preserving healthy cells. The plant's constituents, including saponins, tannins, flavonoids, and lutein, promote apoptosis, induce cell cycle arrest at the G0/G1 phase, and impede cancer cell viability. Moreover, tin nanoparticles generated from its aqueous extract exhibit antioxidant capabilities and cytotoxicity toward breast cancer cells, notably in a manner that is dependent on both time and dosage.	MCF-7, MDA-MB-231, MCF10A	2, 3	13,24,25,28,33-36
<i>Catharanthus roseus</i> (Madagascar periwinkle)	It synthesizes anticancer agents such as vinblastine, vincristine, and dimeric indole alkaloids. These chemicals are cytotoxic and impede cancer cell proliferation. These chemicals promote apoptosis and decrease HER-2 expression in breast cancer cells. Incensole acetate derived from the plant's essential oil has a binding affinity for estrogen receptors (ER-positive), comparable to those of fulvestrant and bazedoxifene.	MDA-MB-231 and HER-2-positive breast cancer cell lines	1	24,25,37-41
<i>Ceratonia siliqua</i> (Carob)	It exhibits anticancer characteristics, primarily due to its elevated levels of polyphenols, including myricetin, naringenin, and kaempferol, which promote apoptosis and suppress growth in breast cancer cells. Diethyl ether and ethyl acetate extracts from Carob fruit, which are abundant in polyphenols, specifically impede cancer cell proliferation and trigger apoptosis in MCF-7 cells. Ethanolic extracts exhibited antiproliferative effects on MCF-7, MDA-MB-231, and MDA-MB-436 cells, with MCF-7 exhibiting the greatest sensitivity. Methanolic leaf extracts rich in gallic acid, chlorogenic acid, and flavonoids elicit cytotoxicity and elevate sub-G1 cell populations in a concentration-dependent manner.	MCF-7, MDA-MB-231, MDA-MB-436	1, 2, 3, 4, 6, 7, 8	1,24,25,42-45
<i>Cicer arietinum</i> (Chickpea)	It includes isoflavone, including biochanin A, genistein, formononetin, and trifolylrhizin, which demonstrate significant anticancer properties by suppressing cell growth, causing apoptosis, and influencing cell cycle progression. The mechanism of action of isoflavone derived from sprouted Chickpeas involves the inhibition of breast cancer cell proliferation through the induction of mitochondria-dependent apoptosis, cessation of cell adhesion, and modification of cell shape. These chemicals also diminish EGF-induced p44/42 MAPK signaling and stimulate the NF- κ B pathway, which governs apoptosis and proliferation. Moreover, lectin and protease inhibitor concentrates impede cell division and promote apoptosis throughout the S and G2 phases of the cell cycle.	MDA-MB-231, SKBr3, and MCF-7	1, 2, 3	24,25,42,46-49
<i>Citrullus colocynthis</i> (Bitter apple)	It exhibits notable anticancer properties owing to its bioactive components, especially cucurbitacin glycoside, which triggers apoptosis and cell cycle arrest in breast cancer cells. Cucurbitacin glycoside from leaves interferes with proteolytic complexes crucial for G2/M cell cycle transition. The ethanolic extracts of seeds comprise ethylbenzene and tetrachloroethylene, which are toxic to MDA-MB-231 cells. The ethanol and methanolic extracts of leaves promote apoptosis via caspase-3 activation and the modulation of pro-apoptotic genes. These extracts also modulate cholesterol and triglyceride levels, which are essential for the survival of breast cancer cells.	MCF-7, MDA-MB-231	1, 5, 7	15,24,25,42,50-59
<i>Ficus carica</i> (Fig)	It exhibits significant anticancer effects of flavonoids, tannins, alkaloids, polyphenols, and hydrolytic enzymes. These chemicals are present in Fig leaf and latex extracts and have anticancer properties in breast cancer studies. The mechanism of action involves flavonoids and tannins from Fig leaves, which cause apoptosis and suppress cell proliferation in MCF-7 cells. Figure 4. Latex, abundant in alkaloids and polyphenols, diminishes ERK2, CREB, and AKT2 levels, resulting in reduced tumor proliferation. Bergapten and psoralen cause S-phase cell cycle arrest, facilitate apoptosis, and diminish cell motility in MDA-MB-231 cells.	MCF-7, MDA-MB-231, MCF10A	1, 2, 3, 5	24,25,42,60-65
<i>Glycyrrhiza glabra</i> (Licorice)	The anticancer properties of glycyrrhizin are chiefly attributable to its constituent glycyrrhizin and its derivatives, which promote apoptosis, impede cell proliferation, and prevent metastasis. Glycyrrhizin and its derivatives activate caspases to promote apoptosis and block FAK/Rho signaling to prevent metastasis in MDA-MB-231 cells. Furthermore, glycyrrhizin elevates miR-200c and e-cadherin levels, thereby diminishing cancer cell invasiveness. Glycyrrhetic acid modulates VEGFR2, triggers mitochondria-dependent apoptosis, and influences the p38 MAPK-AP1 pathway, thereby affecting tumor proliferation and metastasis. Root extract affects the viability of 4T1, MCF-7, and HER-2 cells by generating morphological alterations.	MDA-MB-231, BT549, 4T1, MCF-7, HER-2	3, 4, 5, 7	24,25,42,66-69,71-73

Table 1. continued				
Plant	Bioactive compounds and their mechanism of action	Cell lines	Divisions	References
<i>Hordeum vulgare</i> (Barley)	Anticancer chemicals, including gramine and hordenine, that demonstrate substantial anticancer efficacy, especially against breast cancer cells. Bioactive constituents inhibit cancer cell proliferation and promote apoptosis. Gramine activates the adiponectin receptor 2 pathway, thereby reducing MDA-MB-231 and MCF-7 cell proliferation. Hordenine derived from germinated Barley seed initiates extrinsic apoptosis, whereas palmitic acid promotes apoptosis by activating caspase-3, Bax, and p53. Moreover, Barley bran polyphenols diminish the viability of breast cancer cells, whereas fermented Barley extract exhibits potential in inhibiting the progression of non-invasive breast cancer to an invasive form.	MDA-MB-231, MCF-7, EMT6/p, TNBC	2	11,24,25,42,48,74-76
<i>Myrtus communis</i> (Myrtle)	Essential oils and extracts exert anticancer effects, particularly by triggering apoptosis in breast cancer cells. Mode of action: the essential oil, which is abundant in alpha-pinene, 1,8-cineole, and linalool, exerts cytotoxic effects on breast cancer cells such as MCF-7. Significantly, 1,8-cineole specifically triggers apoptosis in cancerous cells while sparing healthy cells. β -ionone is a significant component of the essential oil, and it can prevent cancer growth both <i>in vitro</i> and <i>in vivo</i> . Myrtucommulone derived from the leaves augments the activity of caspase 3 and 9, resulting in PARP cleavage and apoptotic DNA fragmentation. Methanolic extracts exert significant cytotoxic effects on breast cancer cell lines.	MCF-7, MCF10A	All	24,25,42,67,77-81
<i>Nigella sativa</i> (Black cumin)	Essential components such as thymoquinone, thymol, and thymoquinone, which demonstrate significant anticancer properties, especially against breast cancer cells. Thymoquinone diminishes tumor growth, enhances p53 expression, and reduces BRCA1 and BRCA2 levels. It also impedes metastasis by downregulating CXCR4 expression. Nanosized emulsions and silver nanoparticles from <i>Nigella sativa</i> promote apoptosis in MCF-7 cells by modulating Bax, Bcl-2, and Cox-2. Thymoquinone, when administered with tamoxifen, amplifies apoptosis in both ER-positive and ER-negative breast cancer cells. Moreover, nanostructured lipid carriers infused with thymoquinone were effective against MDA-MB-231 and MCF-7 cell lines.	MCF-7, MDA-MB-231	2, 3, 7	24,25,42,63,82,83,85,86
<i>Olea europaea</i> (Olive tree)	The treatment includes bioactive substances, primarily oleuropein (OLE) and oleocanthal, which demonstrate considerable anticancer efficacy. OLE decreased the viability of MCF-7 cells in a dose- and time-dependent manner, promoting apoptosis and decreasing invasiveness. It accomplishes this by regulating HDAC4, suppressing ERK1/2 through estrogen signaling, and activating the NF- κ B pathway. In conjunction with doxorubicin, OLE further diminishes NF- κ B, Bcl-2, and survivin, thereby facilitating apoptosis in MDA-MB-231 cells. Oleocanthal treatment inhibits MCF-7 and MDA-MB-231 cell proliferation while sparing normal cells. Moreover, apigenin and hydroxytyrosol inhibit growth factor receptors, resulting in cell cycle arrest at the G2/M and G1/S phases in MCF-7 cells.	MCF-7, BT474, MDA-MB-231	1, 2, 3, 4, 7, 8	2,24,25,42,87-91
<i>Rosmarinus officinalis</i> (Rosemary)	Bioactive substances such as carnosic acid, rosmarinic acid, oleanolic acid, betulinic acid, and flavonoids, all of which have considerable anticancer effects. Rosemary essential oil and its constituents promote apoptosis in breast cancer cells, specifically MCF-7 and TNBC cells, such as MDA-MB-231 and MDA-MB-468. Carnosol and uric acid suppress NF- κ B pathways, obstruct carcinogenesis, and impede Cox-2 production, which is essential for cancer growth. Rosmarinic acid modulates apoptosis-associated genes and is particularly potent against TNBC cells. Silver nanoparticles produced from Rosemary exert lethal effects on breast cancer cells, inhibiting disease development.	MCF-7, MDA-MB-231, and MDA-MB-468	1, 8	10,24,25,42,63,92-96
<i>Silybum marianum</i> (Milk thistle)	Contains silymarin and its active constituent silibinin, which exhibit significant anticancer properties, particularly against breast cancer. Silymarin causes cell cycle arrest and death in MDA-MB-468 and MCF-7 breast cancer cells by upregulating p53 and downregulating VEGF and matrix metalloproteinases. Silibinin exhibits a dose- and time-dependent effect on the inhibition of MCF-7 cell proliferation, demonstrating synergistic effects when administered alongside chemotherapeutic drugs, such as doxorubicin, carboplatin, and cisplatin. The encapsulation of silibinin in nanoparticles has demonstrated increased apoptotic efficacy.	MDA-MB-468, MCF-7	2, 3, 4, 5, 6, 8	12,24,25,100-102
ROS: Reactive oxygen species, PARP: Poly (ADP-ribose) polymerase, TNBC: Triple-negative breast cancer, VEGF: Vascular endothelial growth factor, ER: Estrogen receptor, HER-2: Human epidermal growth factor receptor-2.				

In Cyprus, *Artemisia annua* is a notable species and is categorized as CA. As shown in Figure 3, this plant belongs to division 6, indicating its presence in a specific region of the island.²⁵ The extract from *Artemisia annua*, which is particularly enriched through acetonitrile maceration, contains flavonols such as chrysosplenol D and cacticin, which trigger apoptosis and cell cycle arrest, thereby eliminating MDA-MB-231 and MCF-7 breast cancer cells.^{31,32} Moreover, polyphenols from the extracts of *Artemisia annua* exhibit a tendency to act as anti-cancer agents by notably killing CD44, Oct-3/4, catenin, and MMP-9 proteins, which

are associated with radio resistance in MDA-MB-231 human breast cancer cells.³⁰ Coactive substances like syringaldehyde and quercetin from *Artemisia annua* have an inhibitory function, leading to the prevention of the migration of MDA-MB-231 cells toward endothelial cells.²⁹ Dihydroartemisinin, the main active metabolite of artemisinin from *Artemisia annua*, slows down cell division, induces apoptosis, and prevents tumor expansion in breast cancer cells. When administered in conjunction with dihydroartemisinin, docetaxel enhances the effectiveness of chemical therapy.¹⁶ Artesunate, another derivative of

artemisinin, shows remarkable antitumor activity mainly via apoptosis and cell cycle arrest in both triple-negative breast cancer (TNBC) and HER-2-enriched cell lines.^{9,16} These substances further suppress cancer cell growth by inducing reactive oxygen species (ROS)-dependent G2/M-phase cell cycle arrest and ROS-independent G1 phase cell cycle arrest.⁹



Figure 1. Eight phytogeographic regions in Cyprus from division 1 to division 8.²⁵



Figure 2. *Aloe vera* (*Aloe barbadensis* Mill.) photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Aloe vera* in Cyprus. Areas marked in yellow indicate divisions where *Aloe vera* casually grows (CA).²⁵ Photographer: G. N. Hadjikyriakou.

Calendula officinalis

Calendula officinalis, commonly referred to as Marigold, is a botanical marvel celebrated for its multifaceted medicinal properties within the Asteraceae family.³³ Embraced in traditional medicine across diverse cultures, *Calendula officinalis* flowers and leaves are used to treat an array of ailments, including poorly healed wounds, bruises, rashes, burns, and gastrointestinal discomfort.^{13,34,35} Notably, extracts from flowers, leaves, and roots exhibit promising antitumor effects both *in vitro* and *in vivo*, accentuating their potential in cancer management.^{28,34} The local people of Cyprus have observed that this medicinal plant has a therapeutic effect by crushing its flowers, extracting the oil, and applying it to inflamed and injured areas. Additionally, brewing and drinking dried calendula flowers as tea can alleviate stomach disorders like stomach ulcers and gastritis.²⁴ Cyprus classifies *Calendula officinalis* as CA; it primarily thrives in divisions 2 and 3, which encompass specific regions (Figure 4) across the island. This medicinal plant appears to be a promising candidate in Cyprus, warranting further investigation for its potential role in combating breast cancer.²⁵ The MDA-MB-231 breast cancer and MCF10A normal cell lines were used to evaluate the activity of *Calendula officinalis* flowers extract. Notably, this extract demonstrated approximately 40% cancer cell survival while maintaining the viability of normal breast cells.^{28,36} Examining the extract's chemical structure revealed the presence of numerous bioactive compounds like saponins, tannins, and flavonoids, which are believed to collectively contribute to its cytotoxicity. Additionally, the investigations revealed that a semi-purified *Calendula officinalis* flower extract induces apoptosis



Figure 3. *Artemisia annua* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Artemisia annua* in Cyprus. The yellow area indicates the division where *Artemisia annua* grows casually (CA).²⁵ Photographer: G. N. Hadjikyriakou.

and cell cycle arrest, particularly in the case of the MCF-7 cell line.²⁸ Additionally, in a study conducted with ultrasonic-assisted extraction of dried flowers and leaves in methanol, it was observed that the cell lethality and selectivity of the flower extract were higher than those of the leaf extract.^{34,36} Scientists have discovered that extracts of *Calendula officinalis* cause cell death in the G0/G1 phase and kill MCF-7 cells.³⁴ Another crucial discovery was that scientists used the aqueous extract of *Calendula officinalis* to produce “green-synthesized tin nanoparticles,” which have demonstrated effective anti-breast cancer agents (inhibitory effects) for the MCF-7 cell line because of their antioxidant effects. These nanoparticles exhibited time- and dose-dependent cytotoxicity, suggesting their potential as adjuvant therapeutic chemotherapeutic agents.³⁵ The methanolic leaf extracts of *Calendula officinalis* selectively killed different types of breast cancer cells while having little effect on healthy cells.³³ Notably, lutein, a chemical isolated from *Calendula officinalis*, is more effective at killing TNBC cells than other types of cancer cells, suggesting its potential use as targeted therapy.¹³

Catharanthus roseus

Catharanthus roseus, also known as Madagascar periwinkle, is a rose-like plant belonging to the Apocynaceae family that is native to Madagascar. The flowering is more visible at the axillary, giving the plant a white-red bloom spectrum. Additionally, *Catharanthus roseus*

is a highly adaptable plant, and its rapid spread and growth can support its growth in a variety of climates.³⁷ People not only value this plant for its decorative beauty, but also for its aromatic and medicinal qualities.^{37,38} Therefore, the traditional method involves immersing the dry leaf or entire plant of *Catharanthus roseus* in boiling water and then consuming the resulting decoction to treat diabetes.³⁸ In addition, local people have been using liquid extracts of leaves or entire plants as long-term treatments for cancers such as breast, throat, lung, and esophageal cancers.^{37,38} Local people have been using *Catharanthus roseus* orally for its hypoglycemic effect, which has been known for its cancer benefits for many years and has greatly contributed to the production of modern cancer drugs.²⁴ *Catharanthus roseus* occupies a notable place in the flora of Cyprus, characterized by its CA status. As a location, division 1 designates its occurrence in specific regions of Cyprus, providing insights into its distribution within the island (Figure 5).²⁵ Recently, medicinal plants, especially *Catharanthus roseus*, which is a great source of anticancer compounds, namely vinblastine and vincristine, have become very important tools in the fight against breast cancer.^{37,38} Studies based on both animal and cellular models have extensively examined the effectiveness of *Catharanthus roseus*. A group of researchers wanted to make PLGA-based polymeric nanoparticles that were full of *Catharanthus roseus*. These particles can bind to HER-2 overexpression for the treatment of breast cancer. The results indicated that both PLGA-PEG *Catharanthus roseus* (PLGA-PEG CR) formulations have cytotoxic effects, with sustained release observed in PLGA-PEG CR G68 and downregulation of HER-2 expression induced by PLGA-PEG CR F68.³⁷ In another study, the effect of incense acetate (IA), a compound of *Catharanthus roseus* essential oil and its nanoemulsion, on breast cancer cells. The IA-based nanoformulation



Figure 4. *Calendula officinalis* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Calendula officinalis* in Cyprus. Areas marked in yellow indicate divisions where *Calendula officinalis* grows casually (CA).²⁵ Photographer: G. N. Hadjikyriakou.



Figure 5. *Catharanthus roseus* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Catharanthus roseus* in Cyprus. The yellow area indicates the division where *Catharanthus roseus* grows casually (CA).²⁵ Photographer: Authors.

demonstrated cytotoxicity against breast cancer cell lines, with “*in vitro*” improvements that were promising and nearly comparable to those obtained in clinics and biochemical research studies. Docking studies showed that IA had estrogen receptor-positive (ER-positive) binding affinity to fulvestrant, bazedoxifene, and cyclophosphamide. This means that IA could be used to treat only ER-positive breast cancer once it has been proven to work in the clinic and received official approval.³⁹ Furthermore, the alkaloid and phenolic content of *Catharanthus roseus*, combined with three newly isolated dimeric indole alkaloids, including 14', 15'-didehydrocyclovinblastine, 17-deacetoxyvinamidine, and 17-deacetoxyvinblastine, contributes to its anticancer properties by inhibiting cell proliferation and inducing apoptosis on the MDA-MB-231 human breast cancer cell line.³⁸ Furthermore, *in vivo* studies reported a synergistic effect of combining *Catharanthus roseus* with *Phyllanthus urinaria*, as the chemotherapy regimen consisting of irinotecan, 5-fluorouracil, and leucovorin exhibited an immunomodulatory effect upon inhibiting the proinflammatory cytokines interleukin-17A (IL-17A) and IL-6.^{40,41}

Ceratonia siliqua

Ceratonia siliqua (Carob tree) is a member of the Fabaceae family. It is a perennial evergreen tree that grows in the Mediterranean region. The highly esteemed Carob fruit, also known as a pod, is widely used as food due to its high nutritional value and as a versatile raw material in industry. This pod, which is entirely made of pulp and seeds, contains bioactive compounds beneficial for human health. In addition, although the leaves of the Carob tree are not appreciated enough for their health benefits, they contain a large number of useful compounds that have been widely used in medicinal practice.¹ *Ceratonia siliqua* is utilized by the population of Cyprus for its nutritional benefits, including the consumption of raw fruits, conversion of dried fruits into flour to alleviate gastrointestinal issues and diarrhea in infants, production of Carob molasses, and incorporation of Carob molasses into various culinary recipes.^{24,42} *Ceratonia siliqua* occupies a significant place in the flora of Cyprus, as indicated by its IN status. Distributed across divisions 1, 2, 3, 4, 6, 7, and 8, as illustrated in Figure 6, this plant's presence spans various regions of the island and thrives in diverse habitats.²⁵ A comprehensive study exploring the medicinal potential of Carob plants native to Cyprus for the treatment of breast cancer identified high contents of myricetin, naringenin, and kaempferol, which are prominent polyphenols recognized for their anti-cancer activity, in diethyl-ether and ethyl acetate extracts obtained from ripe whole Carob fruit. These extracts exhibited specific activity against the MCF-7 breast cancer cell line. They also selectively inhibit proliferation and induce apoptosis. While exhibiting these effects, they have a minimal effect on normal cells.^{43,44} Yet another study examined the ethanolic extract of *Ceratonia siliqua* extract (CSEE), which includes an array of phenolic compounds and flavonoids, in which, in addition to naringin, a significant amount was represented. CSEE treatment inhibited the proliferation of MCF-7, MDA-MB-231, and MDA-MB-436 breast cancer cells. It is clear that among these three cell lines, MCF-7 was the most responsive to CSEE treatment, whereas MDA-MB-231 and MDA-MB-436 cells exhibited fewer sensitive reactions.¹ Other than these components, the Carob leaves, pulp, and seeds contain gallic acid, chlorogenic acid, syringic acid, p-coumaric acid, m-coumaric acid, quercetin 3-O-rutinoside, and quercetin, which contribute to the nutrition of Carob pods. Upon the observation of a methanolic leaf extract of Carob, rich in significantly high amounts of these phenolic compounds, total flavonoids, and condensed tannins, it was observed that Carob extract showed a dose-



Figure 6. *Ceratonia siliqua* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Ceratonia siliqua* in Cyprus. Areas marked in green indicate divisions where *Ceratonia siliqua* grows indigenously.²⁵ Photographer: C. S. Christodoulou, and G. N. Hadjikyriakou.

dependent cytotoxic effect on MDA-MB-231 human breast cancer cells. Moreover, the leaf extracts exhibited a notable capacity to inhibit cell proliferation, resulting in an increase in the proportion of cells at the sub-G1 stage compared with the pulp extracts.^{43,45}

Cicer arietinum

Cicer arietinum, a member of the Fabaceae family, is commonly referred to as desi Chickpea. In nature, the flower is noticeable by its small size and colorful seed coats of red, green, brown, and black. Global diets incorporate Chickpeas, primarily from Asia, in various forms such as cooked grains or flour.^{46,47} Many bioactive compounds, especially isoflavone, are known for their strong anticancer effects by binding to ERs and working with estrogenic polyphenols.⁴⁶ Chickpeas have traditional medicinal value and have been used historically to treat health concerns ranging from hypertension to osteoporosis.⁴⁷ In Cyprus, *Cicer arietinum* is incorporated into the daily diet. Before serving as appetizers, these Chickpeas undergo various culinary processes such as boiling. Moreover, people consume the raw seeds of this plant for their believed aphrodisiac properties and to alleviate hoarseness.^{24,42} Figure 7 shows that *Cicer arietinum* classified under the CA status is significant in the flora of Cyprus, spanning divisions 1, 2, and 3. The relevance of this approach to breast cancer research in Cyprus is compelling. This introduction outlines the significance of *Cicer arietinum* in breast cancer research within Cyprus, focusing on its botanical traits and island-wide distribution.²⁵ For example, research using *Cicer arietinum* on breast cancer has shown that sprouted Chickpeas increase the levels of isoflavone in black Chickpeas, which lowers the growth of MDA-MB-231 cancer cells. The isoflavone mentioned include biochanin A, genistein, formononetin, calycosa, trifolyrhizin, biochanin A-7-Ob-D-glucoside, ononis, and missouri. These isoflavone might stop the SKBr3 and MCF-7 cell lines from moving through the cell cycle or multiplying in a way that depends on time and dose by changing signaling pathways.^{47,48} They also have strong antitumor effects on MDA-MB-231 cancer cells, causing mitochondrial-dependent apoptosis, stopping cell growth, stopping cell adhesion, and changing the shape of the cells.⁴⁹ Here, the study identified that the NF-κB signaling pathway, which regulates critical



Figure 7. *Cicer arietinum* photograph in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Cicer arietinum* in Cyprus. Areas marked in yellow indicate divisions where *Cicer arietinum* grows casually (CA).²⁵ Photographer: G. N. Hadjikyriakou.

biological processes like proliferation and apoptosis, as a common active pathway in MDA-MB-231 cancer cells.^{46,49} Lectin from Chickpeas prevents MCF-7 cells from dividing and apoptosis in the S and G2 phases of the cell cycle. On the other hand, protease inhibitors effectively kill MDA-MB-231 breast cancer cells, possibly by interfering with certain cellular processes or pathways.⁴⁸

Citrullus colocynthis

Citrullus colocynthis, classified as Bitter apple or colocynth, is a subtropical desert viny plant that grows in arid and sandy soil across the Mediterranean and Asian Basins as part of its global distribution.⁵⁰ Bitter apple is a typical wild species of the family Cucurbitaceae, and it is well-known for its variety of genetic strains.⁵¹ *Citrullus colocynthis* fruit, which has a naturally spherical yellowish-brown appearance, contains various bioactive elements that have beneficial effects on human health.⁵² Traditional medicine uses the roots, stems, fruits, and leaves of this medicinal plant to alleviate a variety of health problems, including bacterial infections and cancer.^{15,53,54} The local people of Cyprus primarily use this medicinal plant by boiling its roots and then drinking it after cooling down for its purgative effect.^{24,42} *Citrullus colocynthis* occupies a leading place among Cyprus's flora species under the status of IN. As shown in Figure 8, this medicinal plant is distributed across divisions 1, 5, and 7 of the island.²⁵ In studies, both ethanolic and aqueous extracts from fruit flesh showed great potential, with over 50% reduction in cell survival rates observed in MCF-7 breast cancer cell lines.^{52,53,55} Moreover, cucurbitacin glycoside, derived from the leaves of *Citrullus colocynthis*, has been identified as an effective agent for treating human breast cancer cells because it causes apoptosis and cell cycle arrest.^{15,50,53,56} The cells, which contained cucurbitacin glucosides, showed these effects as they quickly reduced the levels of these proteolytic complexes that are essential for the regulation of G2 progression and subsequent M-stage beginning.⁵⁰ Additionally, the ethanol extract of seeds was found to be toxic to MDA-MB-231 cells via the presence of components such as ethylbenzene and tetrachloroethylene¹⁵, while the ethanol extract of leaves induced cell death in the MCF-7 cells via the regulation of the expression of pro-apoptotic (*Bax*) and *caspase-3* genes.^{57,58} Methanolic extracts of *Citrullus colocynthis* leaves appeared to be very promising as breast cancer therapy agents, as they demonstrated dose- and time-dependent cytotoxic effects by increasing caspase-3 expression



Figure 8. *Citrullus colocynthis* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Citrullus colocynthis* in Cyprus. Areas marked in green indicate divisions where *Citrullus colocynthis* grows indigenously.²⁵ Photographer: C. S. Christodoulou, and G. N. Hadjikyriakou.

level MCF-7 cells and slowing down cell proliferation markers like Ki67 in a dose-dependent manner.^{54,59} In addition, higher cholesterol levels stimulated the development of breast cancer. Breast cancer cells can be altered to downregulate de novo the fatty acid synthesis pathway, which is thus interfered with via the use of *Citrullus colocynthis* leaf extract to regulate cholesterol and triglyceride levels, which were the primary objective.⁵⁹ In addition, experiments demonstrating the effectiveness of evodiamine in combination with berberine demonstrated that MCF-7 breast cancer cells were arrested in the cell cycle while reducing the expression of proteins responsible for cell cycle progression.⁵⁴ Moreover, as exhibited by the *Citrullus colocynthis*-linked silver nanoparticles, the antiproliferative effect in MCF-7 cells was through the interference of both cholesterol and triglyceride levels, thus showing potential in the management of breast cancer advancement.⁵¹

Ficus carica

Ficus carica, commonly known as the Fig, belongs to the Moraceae family.⁶⁰ The figure, as a seasonal fruit, is one of the earliest cultivated species and is an important crop globally, flourishing within the natural ecosystems of the Mediterranean basin.^{61,62} *Ficus carica* has a variety of applications in Cypriot traditional medicine, including its use as a remedy for insect bites by preparing leaf decoctions and applying them externally to affected areas. Additionally, the latex derived from cutting branches is used topically to alleviate skin infections, demonstrating the plant's therapeutic efficacy within local healing practices.^{24,42} The classification of *Ficus carica* is shown in Figure 9, where IN indicates its widespread distribution across divisions 1, 2, 3, and 5. Exploring the therapeutic potential of *Ficus carica* in breast cancer research holds promise for uncovering novel treatments deeply rooted in Cyprus's

botanical heritage.²⁵ The ethanol extract of *Ficus carica* leaves exhibited notable anticancer activity against MCF-7 cells. The presence of secondary metabolites, specifically flavonoids and tannins, in Fig leaf and fruit extracts is responsible for this effect.^{61,63} Using *Ficus carica* leaf latex, which is full of alkaloids, polyphenols, and hydrolytic enzymes, to treat MDA-Mb-231 cells decreased the levels of ERK2, CREB, and AKT2. This suggests that the latex can be used to treat breast cancer. The Fig latex also prevented the growth of large tumors without affecting hematologic parameters or inflammation. This is because it has antioxidant, anti-inflammatory, and pro-apoptotic properties. In experiments with rats, *Ficus carica* latex extract reduced breast tumor volume and size. It suggests that reduced angiogenesis, mitotic activity, and necrosis are potentially mediated by its active ingredients.^{60,64,65} A different study found that treating MDA-MB-231 cells with *Ficus carica* extract prevented them from multiplying while leaving MCF10A normal breast epithelial cells alone. Bergapten and psoralen, two active ingredients in *Ficus carica* leaves, were found to have similar anticancer effects, especially in MDA-MB-231 cells. In treated cells, these effects included increased expression of apoptosis-promoting genes, cell-cycle arrest at the S phase, and reduced cell mobility.^{62,63}

Glycyrrhiza glabra

The pharmaceutical, nutritional, and occasionally even tobacco industries highly value the perennial herb known scientifically as *Glycyrrhiza glabra*, a member of the Fabaceae family. The Greek meaning of its name, glycosmis (sweet) and riza (root), add to its significance. The first thing to think about is *Glycyrrhiza glabra*, which is usually recognized by its smooth, crack-free fruit and glycyrrhizin, which is its main chemical and is over 50 times sweeter than sugar.⁶⁶ Interestingly, glycyrrhizin production rises as the plant's age increases in years.⁶⁷ Herbal remedies have been studied for the treatment of various diseases based on the healing properties of their roots and stems.^{66,67} Studies have demonstrated its traditional value, revealing anti-fungal, antihepatotoxic, and anti-cancer effects due to its bioactive compounds.⁶⁸ The local people of Cyprus generally use *Glycyrrhiza glabra* daily due to its sweetening and flavoring properties. In addition, the preparation of syrup from the roots serves as a cough suppressant.⁴² The flowers of Cyprus hold a significant role in the medicinal production of the *Glycyrrhiza glabra* plant, known as IN. Its presence spans divisions 3, 4, 5, and 7, as shown in Figure 10, indicating its distribution across specific regions of the island.²⁵ Research has

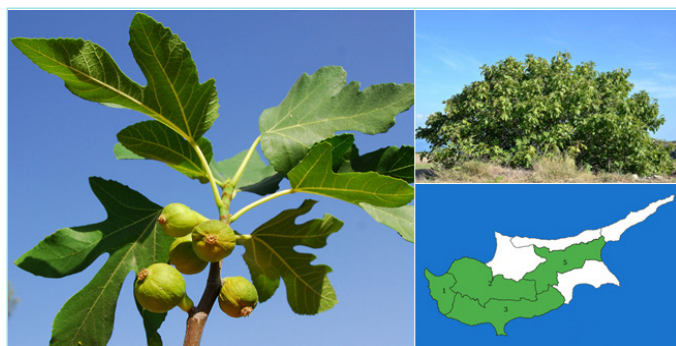


Figure 9. *Ficus carica* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Ficus carica* in Cyprus. Areas marked in green indicate divisions where *Ficus carica* grows indigenously.²⁵ Photographer: G. N. Hadjikyriakou and C. S. Christodoulou.

demonstrated that *Glycyrrhiza glabra* extract regulates the metabolism of genotoxic estrogen, enhance the metabolism of harmless estrogen, enhance detoxification enzymes, prevents DNA damage, and ultimately suppresses inflammation.⁶⁹ As the same cancer cell line was commented the glycyrrhizin derivative, 3-acetyl-18-glycyrrhethinic-30-methyl ester, triggered apoptosis in the same cancer cell line by activating caspases and altering the conformation.⁷⁰ Furthermore, reports have suggested that glycyrrhizin inhibits metastasis, invasion, and new blood cell formation in human MDA-MB-231 cancer cells. Reports have indicated that inhibition of the FAK/Rho signaling pathway achieves this effect.⁷¹ On the other hand, mean glycyrrhizin is effective at stopping the growth of MDA-MB-231. It even increases the levels of miR-200c and e-cadherin, which are known to prevent cancer cells from spreading and invasiveness.^{71,72} The root extract of *Glycyrrhiza glabra* influences the model by reversing the viability and inducing morphological changes in the mammary cell lines 4T1, MCF-7, and HER-2. Additionally, it enhances the phosphorylation level of Bcl. Furthermore, glycyrrhizin targets growth inhibition, followed by breast tumor outgrowth and pulmonary metastasis via *p38 MAPK-AP1* gene pathway modification.⁷² Findings indicate two things: Firstly, the watery extract of Licorice contains phytoestrogen compounds that can help prevent cancer. Secondly, the use of Licorice compounds along with chemotherapeutic agents is better for the treatment.⁶⁸ Patients with breast cancer can also use glycyrrhethinic acid from *Glycyrrhiza glabra* root as an alternative to doxorubicin, which affects the mitochondrial-dependent apoptotic pathway and downregulates the VEGFR2 pathway.⁷³

Hordeum vulgare

Barley is a cereal plant type with the scientific name *Hordeum vulgare* and belongs to the family Poaceae. It has inherited the ancient belief of traditional medicine that its properties are cold and dry, due to which it has a purifying power.^{11,48,74} As the fourth largest cereal crop worldwide, Barley has been used for years not only as animal feed and in alcoholic brewing but also as a diet health supplement because it contains many natural nutrients like Barley juice and young leaves, which are used as its plant metabolite products.⁷⁴ Traditionally, it has been used to treat a wide range of diseases, such as diabetes, respiratory illnesses, arthritis, and obesity.^{11,48,74} Other uses of Barley

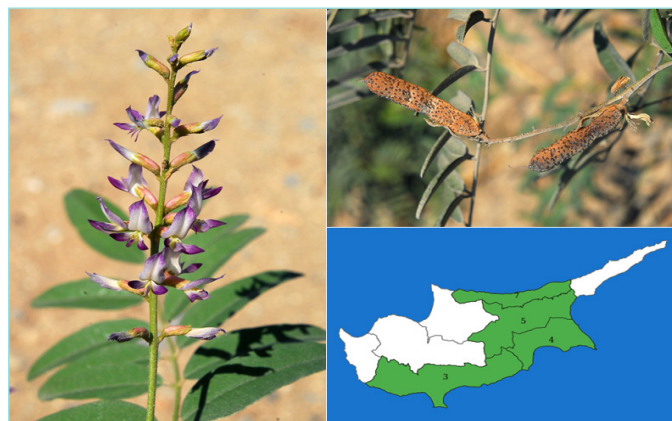


Figure 10. *Glycyrrhiza glabra* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Glycyrrhiza glabra* in Cyprus. Areas marked in green indicate divisions where *Glycyrrhiza glabra* grows indigenously.²⁵ Photographer: C. S. Christodoulou, and G. N. Hadjikyriakou.

include its flowers as a contraceptive and dried seeds as an infusion to exhibit galactagogue properties.¹¹ The local people of Cyprus used *Hordeum vulgare* for various purposes. Its most common use is to grind Barley and mix it with olive oil, milk, mallow, and nettle to make a paste. People apply this poultice to aching joints, anticipating its pain-reducing and antirheumatic effects.^{24,42} The dynamic checklist “Flora of Cyprus” categorizes *Hordeum vulgare* as CA and reports its presence in division 2 (Figure 11).²⁵ A study on Barley grass extract showed that it can help fight breast cancer. This effect occurred by raising the levels of ROS in MDA-MB-231 breast cancer cells, which led to cell death. In addition, gramine, an indole alkaloid that is normally found in *Hordeum vulgare*, can stop MDA-MB-231 and MCF-7 cell growth by activating adiponectin receptor 2.⁴⁸ This is what this receptor does to the body. Further investigation using a methanol extract from germinated seeds of *Hordeum vulgare* (MGHV) will shed more light on its potential to combat breast cancer in TNBC cells. The high content of hordenine, a chemical with anticancer mechanisms that binds specifically to caspase-8 in MDA-MB-231 cells, is primarily responsible for MGHV's ability to trigger the extrinsic pathway of apoptosis without causing DNA damage.⁷⁴ Barley bran stands out among other cereal grains because it is rich in polyphenols (which include saponins, tannins, flavonoids, phenols, alkaloids, terpenoids, steroids, and carbohydrates). In addition to breast cancer treatment, it plays an important role in preventing breast cancer initiation and progression. Various Barley bran extracts cause a dose-dependent reduction in the viability of breast cancer cells. For instance, n-hexane and methanol extracts can disrupt the proliferation of both MCF-7 and EMT6/p breast cancer cells. The aqueous extract inhibited only EMT6/p breast cancer cells. Apoptosis-related proteins like caspase-3, 9, Bax, and p53 were activated by palmitic acid in another experiment. This stopped the growth of MCF-7 breast cancer cells. Studies conducted using fermented Barley extract concluded that it is not toxic to healthy cells and has the potential to prevent the progression of non-invasive breast cancer into invasive breast cancer.⁷⁵ Furthermore, scientists have noticed that the bioactive components of Barley have anti-breast cancer activity, induction of cell cycle arrest, apoptosis progression, and blockage of proliferation. The anti-breast tumor potential of young Barley and its methanolic extract is multifaceted, including mechanisms of cell apoptosis and cell growth regulation. The downregulation of tumorigenesis and upregulation of apoptosis, demonstrated by an increase in caspase-3/caspase-7 activity and a decrease in Ki67 levels in animal models, are evident.⁷⁶

Myrtus communis

Myrtus communis, commonly known as Myrtle, a prominent member of the Myrtaceae family, is a significant aromatic and medicinal species found abundantly across Mediterranean regions.⁷⁷⁻⁷⁹ It has a perennial bush-like form, typically with characteristic white flowers and blue ball-shaped fruits.^{67,79} Because of its diverse bioactive constituents, this herbaceous plant has been integral to ancient healing practices, particularly in Greek and Unani medicine. Studies have underscored its multifaceted pharmacological effects, ranging from antimicrobial and antifungal to hepatoprotective and anticancer activities.^{77,78} Additionally, daily culinary applications of *Myrtus communis* include flavoring foods and wines.⁷⁷ *Myrtus communis* is a plant that the local people in Cyprus respect for its versatile therapeutic properties, as well as its daily consumption throughout the season. People often prepare its leaves as infusions or decoctions, make them into tea, and consume them for their antihypertensive, antihyperglycemic, and cholesterol-lowering properties. Additionally, when dried in the shade and ground



Figure 11. *Hordeum vulgare* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Hordeum vulgare* in Cyprus. The yellow area indicates the division where *Hordeum vulgare* grows casually (CA).²⁵ Photographer: G. N. Hadjikyriakou.

into a fine powder, the leaves work topically to relieve diaper rash. Additionally, consumption of its fruits has been shown to have an anti-diarrheal effect.^{24,42} Figure 12 shows the distribution of *Myrtus communis* throughout the island (divisions 1, 2, 3, 4, 5, 6, 7, and 8), which earned the status of IN.²⁵ Due to its simple accessibility within the island and its high therapeutic effect, studies and medical advances are important. Studies have shown that *Myrtus communis* essential oil has strong cytotoxic effects against breast cancer cell lines, stopping tumor cells in a way that depends on the dose.⁷⁸⁻⁸⁰ Furthermore, researchers concluded that this cytotoxic effect specifically targeted cancer cells, inducing apoptotic cell death through DNA fragmentation characteristics.⁷⁸ Another study showed that *Myrtus communis* essential oil is rich in alpha-pinene, 1,8-cineole, and linalool substances. The results also show that these ingredients affect MCF-7 and healthy cells

(MCF10A) in a different manner. The researchers found that α -pinene and linalool were both harmful to both types of cells. On the other hand, 1,8-cineole was only harmful to tumor cells, killing them through apoptosis, without damaging normal cells.^{67,79} Another study also mentioned the importance of the essential oil had β -ionone because it had anti-cancer properties and inhibits the growth of breast cancer cells both *in vivo* and *in vitro*.^{80,81} Another study showed that myrtucommulone from *Myrtus communis* leaves enhanced the activity of caspases 3 and 9, leading to poly (ADP-ribose) polymerase cleavage and apoptotic DNA fragmentation. Moreover, the methanolic extracts of *Myrtus communis* exhibited strong anticancer activity against MCF-7 cell lines.^{67,78}

Nigella sativa

Nigella sativa, also known as Black cumin, is a plant that belongs to the Ranunculaceae family.^{82,83} As an integral part of the healing process, *Nigella sativa* has been used in the medical systems of many cultures and cuisines.^{82,84} Many active compounds, including thymol, dithymoquinone, thymoquinone, and thymohydroquinone, contribute to its broad spectrum of pharmacological functions, including anti-inflammatory, antihypertensive, antioxidant, antidiabetic, antimicrobial, and anticancer properties.^{63,83,85,86} *Nigella sativa* use among Cyprus's population encompasses diverse medicinal applications. Local people incorporated decoction tea derived from the seeds internally because of its purported antihyperglycemic, cholesterol-lowering, and carminative properties.⁴² *Nigella sativa* is a noteworthy subject in the context of medicinal plants found in Cyprus. This plant, classified as CA in divisions 2, 3, and 7 (Figure 13), is consistent with the vibrant colors of Cyprus's natural landscape during the warmer months. *Nigella sativa* has a rich historical and cultural significance and is revered for

its numerous health benefits and therapeutic properties.²⁵ Numerous studies have investigated the potential of *Nigella sativa* in the treatment of breast cancer. The watery and rough extracts of *Nigella sativa* are effective at stopping the growth of MCF cell lines. Histological studies on DMBA-treated rats have shown that *Nigella sativa* can activate breast cells and stop cancer cell growth.^{63,86} Thymoquinone is a key compound in *Nigella sativa* seed oil that has been shown to reduce the size of tumors and change gene expression, including increasing *p53* expression and decreasing *BRCA1* and *BRCA2*.^{63,85,86} Furthermore, the application of nanosized emulsions and aqueous extracts from *Nigella sativa* can induce apoptosis in MCF-7 cells. Consequently, the application of nanosized emulsions and aqueous extract of *Nigella sativa* prevents MCF-7 cell viability.^{63,83,85} Additionally, studies have demonstrated that *Nigella sativa* silver nanoparticles trigger programmed cell death through the up- or downregulation of Bax, Bcl-2, and cyclooxygenase-2 (Cox-2).^{63,83} In addition, thymoquinone can inhibit metastasis by suppressing CXCR4 expression and decreasing movement and metastasis in breast cancer cell lines.^{82,85} When thymoquinone is combined with the common drug tamoxifen, they work together to kill more cells and cause more cell death in both ER positive and ER negative cells.⁸⁵ In addition, nanostructured lipid carriers loaded with thymoquinone changed the cell genome and killed MDA-MB-231 and MCF-7 cells. In contrast, the pure extract of *Nigella sativa*, which is rich in calcium and magnesium, induces apoptosis by proliferating inside the cells.^{85,86}

Olea europaea

Olea europaea, commonly known as the Olive tree, is an important staple crop in the Mediterranean Basin that has attracted great attention in daily life and medicine because of the oil obtained from its fruits and leaves, which contain various bioactive compounds.^{2,87} Studies dating back to the present day have revealed the existence of antimicrobial, antioxidant, antitumor, and hypoglycemic effects of compounds obtained from this plant's parts.^{2,87,88} *Olea europaea* serves various purposes for local people in Cyprus, including nutrition and medicinal applications. The daily diet incorporates fruits, such as olives, whether black or green. Additionally, its leaves are boiled and consumed for their cholesterol-lowering effects. Olive oil is applied topically to alleviate pain, particularly in cases of sprained ankles. Moreover, it is used to induce emesis by mixing it with milk and consuming it in cases

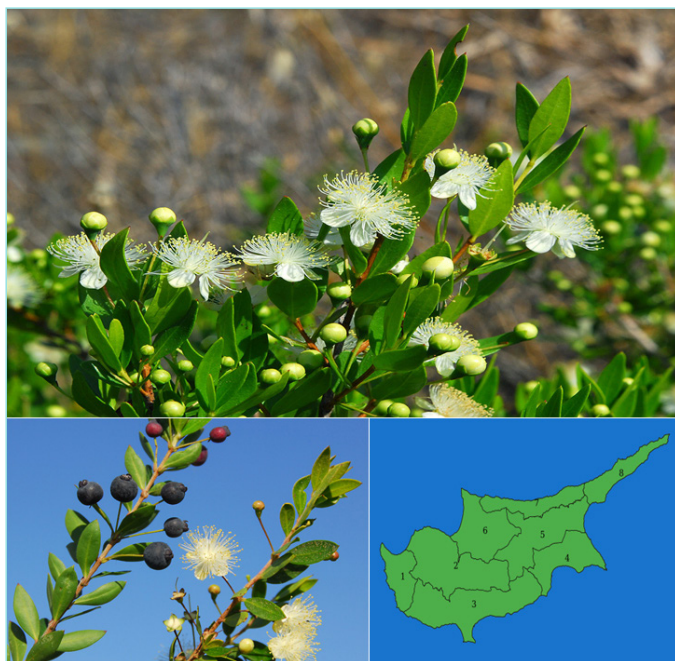


Figure 12. *Myrtus communis* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Myrtus communis* in Cyprus. Areas marked in green indicate divisions where *Myrtus communis* grows indigenously.²⁵ Photographer: C. S. Christodoulou, and G. N. Hadjikyriakou.



Figure 13. *Nigella sativa* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Nigella sativa* in Cyprus. The yellow area indicates the division where *Nigella sativa* grows casually (CA).²⁵ Photographer: G. N. Hadjikyriakou.

of poisoning.^{24,42} *Olea europaea* is a significant flora of Cyprus, denoted by its status as an IN species. The plant distribution, as shown in Figure 14 across divisions 1, 2, 3, 4, 7, and 8 elucidates its prevalence in various regions of the island, ranging from coastal areas to mountainous terrain.²⁵ Studies have investigated the potential anticancer activity of *Olea europaea*, particularly its constituent oleuropein (OLE).^{87,89,90} OLE has been shown to exhibit a dose- and time-dependent decrease in the viability of MCF-7 breast cancer cells and a synergistic inhibitory effect with metformin.² Notably, OLE exhibited apoptotic and anti-invasive effects on MCF-7 cells, modulating histone deacetylase (HDAC) activity. The outgrowth processes, including the diminished level of invasiveness, the boost of apoptosis, and the inhibition of proliferation, are likely to take place in a setting of HDAC4 expression reduction.^{87,90,91} Additionally, OLE initiates the ERK1/2 inhibition action via estradiol communication; additionally, it causes apoptosis through the NF- κ B activation and inactivation pathways in MDA-MB-231 and MCF-7 cell cultures. The combined therapeutic system of doxorubicin and OLE will increase the effectiveness of both drugs and eventually produce downregulation of NF- κ B, Bcl-2, and survivin, which causes the cell to enter the apoptosis process and, hence, a decrease in tumor size in MDA-MB-231 breast cancer. In addition, oleocanthal can block the proliferation of breast cancer cell lines such as MCF-7, BT474, and MDA-MB-231, whereas normal cell growth was not affected.^{88,89,91} Another example of chemopreventive phytochemicals is apigenin in *Olea europaea* leaves, and hydroxytyrosol in both leaves and oils from this plant, which can exert an antitumor effect by targeting growth factor receptors and interleukin pathways that result in cell cycle arrest at the G2/M and G1/S phases of the MCF-7 cell line.^{88,91}

Rosmarinus officinalis

Rosmarinus officinalis is a member of the Lamiaceae family and is one of the most helpful evergreen medicinal plants known as Rosemary.^{92,93} It is a common herb that originated in the Mediterranean.^{93,94} This plant has distinctive needle-like dark green leaves. Due to its valuable medicinal qualities, people not only use its small, needle-shaped dark green leaves for flavoring dishes and seasonings but also for therapeutic purposes. People continue to use it to target various diseases, such as tumor proliferation, and because of its anticancer, antithrombotic, anti-inflammatory, hepatoprotective, antidiabetic, antibacterial, and antihypertensive properties.^{92,93} The local people in Cyprus use *Rosmarinus officinalis* primarily for its multifaceted healing properties. The diuretic action and cholesterol-lowering activity of Rosemary tea regulate digestive system functioning and improve circulatory organ health. Additionally, it serves as an expectorant for patients with bronchitis and is preferred due to its ability to act as an analgesic for those suffering from migraines and/or stomach pain. Additionally, previous studies have shown that inhaling steam from a Rosemary infusion alleviates cold symptoms.^{24,42} In divisions 1 and 8, of Cyprus categorize *Rosmarinus officinalis* as IN (Figure 15). With its aromatic foliage and diverse array of bioactive compounds, Rosemary is a botanical treasure trove, offering potential avenues for exploring its efficacy in combating breast cancer.²⁵ *Rosmarinus officinalis* attracts uric acid, rosmarinic acid, carnosic acid, oleanolic acid, and betulinic acid, all of which have specific effects on cancer cells.⁹³⁻⁹⁵ A dose-response protocol revealed that Rosemary essential oil induces apoptosis in MCF-7 cells. In addition, Rosemary oil has different cytotoxic effects on different types of cancer cells. For example, flavonoids can stop the expression of Cox-2, which is an important enzyme involved in the progression of breast cancer. Moreover, carnosol and uric acid suppress

the DNA-binding activity of cancer cells and block tumorigenesis pathways, including those that NF- κ B modulates.^{63,95} Researchers highlighted the cancer-inhibitory functions of carnosic acid, particularly its ability to destroy tumor-resistant cells. This suggests that it is suitable as a complementary treatment.^{94,95} Furthermore, green synthesized silver nanoparticles derived from Rosemary exert cytotoxic effects on breast cancer, potentially inhibiting the progression of the disease.⁹² Most importantly, studies have shown that rosmarinic acid, a natural polyphenol compound, exerts powerful anticancer activity against TNBC cells such as MDA-MB-231 and MDA-MB-468.⁹⁶ The diverse regulation of numerous apoptosis-related gene sequences, particularly in MDA-MB-468 cells, demonstrates the activity of rosmarinic acid.



Figure 14. *Olea europaea* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Olea europaea* in Cyprus. Areas marked in green indicate divisions where *Olea europaea* grows indigenously.²⁵ Photographer: C. S. Christodoulou, and G. N. Hadjikyriakou.



Figure 15. *Rosmarinus officinalis* photographed in its natural habitat in Cyprus. The map illustrates the geographical distribution of *Rosmarinus officinalis* in Cyprus. The area marked in green indicates the division where *Rosmarinus officinalis* grows indigenously, and the area marked in orange indicates the division where it is naturalized.²⁵ Photographer: C. S. Christodoulou, and G. N. Hadjikyriakou.

These findings underscore the therapeutic potential of Rosemary and its constituents in breast cancer management, particularly in TNBC therapy.¹⁰

Silybum marianum

Silybum marianum, commonly referred to as Milk thistle, is well-known in traditional medicine because of its over 2000 years of use by many people.^{97,98} The Milk thistle, a relative of the Asteraceae family, originated in the mountainous regions of the Mediterranean.^{98,99} People have revered Milk thistle for its efficacy in treating liver and gallbladder-related ailments.^{12,98,100} As a traditional edible phytomedicine, Milk thistle has maintained its significance as a natural remedy for conditions such as hepatitis and cirrhosis.^{12,100,101} Local people in Cyprus use the Milk thistle plant in their daily medicinal practices to treat skin wounds and foot fungal ailments. The plant demonstrates its healing effect by extracting the bulbous part with a hoe and then applying its peels to the affected area while still moistened.²⁴ In Figure 16, the status of *Silybum marianum* is shown as IN and its presence in divisions 2, 3, 4, 5, 6, and 8 of Cyprus. In a previous study, it was observed that silymarin, a powerful polyphenol from the medicinal plant *Silybum marianum*, exhibited significant activity against MDA-MB-468 and MCF-7 breast. These cells respond to silymarin by arresting the cell cycle and inducing apoptotic cell death. Mechanisms involving increased p53 expression and downregulation of vascular endothelial growth factor and matrix metalloproteinase/gelatinase A mediate the effects of this compound.^{12,100} Another study found that silymarin stops the growth of MDA-MB-468 breast cancer cells by stopping them in the G1 cell cycle.⁹⁹ Furthermore, *Silybum marianum* seed aqueous extract is cytotoxic in human breast cancer cell lines, altering cell viability in a manner reliant on time and concentration.¹² Additionally, studies have shown that silibinin, a component of silymarin, exhibits dose- and time-dependent reduction in MCF-7 cells and exhibits synergistic effects when used with

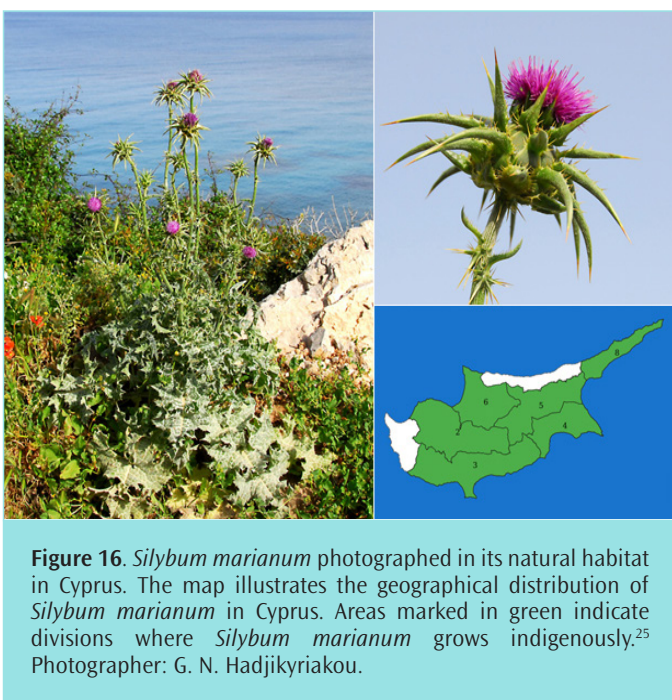
ultraviolet B and other chemotherapeutic agents.¹⁰⁰ Moreover, spherical liposome-encapsulated silibinin nanoparticles have been observed to stimulate MCF-7 cell growth and induce apoptosis more efficiently than drug monotherapy, indicating the potential of nanoparticles in breast cancer treatment.¹⁰² Interestingly, silibinin exhibits a synergistic effect with several chemotherapeutic agents, such as carboplatin, doxorubicin, or cisplatin-all of which significantly depend on estrogens-in breast cancer cells. This further demonstrates the potential of silibinin as an adjunct in breast cancer therapy.¹⁰¹

CONCLUSION

Breast cancer remains one of the leading health threats globally, with its trends in incidence and mortality rates continuing to persist and requiring further improvements in treatment approaches. Treatments such as chemotherapy, radioactive cancer therapy, and surgery are effective; however, they often have severe adverse effects that significantly impact patients' quality of life. As a result, there has been an increasing emphasis on investigating other forms of treatment, particularly those that consider natural sources such as medicinal plants. This review highlights medicinal plants found in Cyprus that have shown some effectiveness as anti-breast cancer agents. Reports indicate that the bioactive compounds in these plants suppress the growth of cancerous cells, induce programmed cell death, and prevent cancer cell spread. These bioactive compounds are potential novel anti-breast cancer agents. Therefore, isolating and standardizing these compounds could lead to new treatment approaches that can be used as effective adjuvant therapy to traditional cancer treatment methods. As a result of further research, integrating such medicinal plants into breast cancer treatment may increase treatment effectiveness, which may improve the well-being of breast cancer patients; this highlights the importance of further studies on the medicinal flora of Cyprus and its potential benefits in oncology.

MAIN POINTS

- Breast cancer remains a major global health issue, with current treatments like chemotherapy, radiation, and surgery, are effective, but they often cause severe side effects that reduce patients' quality of life.
- Due to the side effects of traditional treatments, there is growing interest in exploring natural alternatives, particularly medicinal plants, as cancer treatments.
- This study highlights several plants found in Cyprus that have shown promise as anti-breast cancer agents. Secondary metabolites were explored from medicinal plants as safer alternatives to conventional treatments. These plant compounds have shown promise in preventing cancer cell growth and promoting cell death, offering a potential way to treat breast cancer with fewer side effects.
- If these plant compounds are further researched and standardized, they could become new treatments or be used alongside traditional therapies to improve patient outcomes and well-being, making it important to continue studying Cyprus' medicinal plants for their potential in cancer care.



Footnotes

Authorship Contributions

Concept: G.O., Design: G.Ç., G.O., Data Collection or Processing: G.Ç., Analysis and/or Interpretation: G.O., M.Ç., S.R., Literature Search: G.Ç., Writing: G.Ç., G.O., M.Ç., S.R.

DISCLOSURES

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Wearable Technologies and Psychiatry: Strengths, Weaknesses, Opportunities, and Threats Analysis

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Abstract

As in every other field, technology has an impact on healthcare. As part of technological advancements, wearable technology can guide in identifying illnesses, clarifying diagnoses, and recognizing disease-related hazards early. Considering the advances in wearable technologies impact the mental health field, as they do in all other fields, it is important to assess their implications. Studies in this field and their results will be discussed, and current shortcomings and developments will be revealed. Considering disability, economic burden, and care burden, wearable technology for mental illness is also promising. Although it is generally in the pilot study phase, wearable technology will likely be encountered more frequently in the diagnosis, treatment, and follow-up of mental illnesses with the increase of prospective randomized controlled studies in the near future. The collection of simultaneous and objective data in patients will also benefit evidence-based mental care. Nevertheless, it is imperative to address the matter of patients' privacy and ethical concerns associated with the utilization of wearable technology, given its potential to gather extensive and prolonged data without being driven by specific hypotheses.

Keywords: Wearable technologies, psychiatry, psychiatric care

INTRODUCTION

The World Health Organization has encouraged the integration of assistive technology into health reform initiatives.¹ Today, digital health tools and technology have emerged as promising advancements that substantially assist in identifying disorders and clarifying diagnoses.² Technology has played a key role in providing health services, particularly in domains such as mobile health, monitoring, data collection, warning systems, and record-keeping. Mobile health, previously referred to as wireless e-medicine, now encompasses the utilization of mobile or wireless communication devices in the context of health and healthcare services.³⁻⁶ The wearable devices were first designed by Thorp Edward⁷ and implemented with contributions from Claude Shannon. In recent times, the utilization of wearable technology in mobile health services has enabled the monitoring of various health

issues and has presented novel solutions in both the scientific and industrial fields.⁸⁻¹⁰ Wearable devices enable monitoring, recording, and transmitting physiological signals in non-hospital settings.¹¹ This review comprehensively examines the strengths, weaknesses, opportunities, and threats associated with wearable technology, a rapidly emerging phenomenon in the healthcare domain. Furthermore, it investigates specific instances of wearable technologies within the field of psychiatry. The aim of this review is not to emphasize statistical results but to focus on the advantages and the disadvantages.

Wearable Technology

Wearable technologies encompass electronic devices that are designed to be conveniently worn on the human body or effortlessly integrated into clothing.^{12,13} Wearable technologies that can be attached to or

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integrated with the human skin enable the continuous and unobtrusive monitoring of humans; hence, minimizing disruptions to their everyday routines.¹⁴ Wearable devices include smart gloves, smart watches, patched or patch-like systems, head-worn devices, and eyeglasses. The use of wearable technology enables the concurrent and optimally effective surveillance of patients' physiological parameters, which is a widely sought-after scenario in the healthcare field.^{15,16} Wearable devices encompass primary functionalities, including user interface, communication, data management, energy management, and integrated circuits.¹⁷ These devices are equipped with microprocessors and have been designed to transmit and receive data through the Internet.¹⁸ Wearable technologies, characterized by the integration of microchips and sensors, are experiencing tremendous growth and are poised to exert even more significant influence in the future.¹⁹ With the help of these devices, results such as biological feedback, psychological state assessment, and perception, which are not available on mobile phones and computers can be obtained.²⁰ Interest in this field has increased due to the monitoring, recording, and transmission of physiological signals.

Wearable Technology and Strengths, Weaknesses, Opportunities, and Threats Analysis

Strengths (Opportunities and Strengths) of Wearable Technology

Wearable technology devices enable data collection in the natural environment of patients.²¹ Since these measurements are taken instantaneously and objectively from individuals, they may provide a better source of data than cross-sectional data collected by notification in a clinical setting. It can also be used to monitor treatment results.²² In wearable technology, the data flow is continuous, and data can be collected automatically without the participant having to do anything. This prevents professionals from constantly asking patients for feedback and saves patients from answering questions. These questions continuously asked to the patients may create the risk of that reminding them of the symptoms of the disease, which may lead to changes in behavior and data.^{23,24}

Potential Problems (Weaknesses and Threats) Related to Wearable Technology

In a scoping review on wearable technologies and their reflections on the field of health, it was reported that, in the examined studies, the focus was on the positive aspects of wearable technology, generally omitting negative ones.²⁵ However, despite the advances in wearable technology that have been and will be reflected in the clinical field, there are also a few concerns. One of these concerns is the possibility of collecting vast longitudinal data from individuals without a hypothesis basis for analysis. Big data entails difficult analyses. Physiological signals exhibit high inter-subject and intra-subject variability, challenging the development of generalizable models. Additionally, motion artifacts and other interference sources might dominate the clinically important information embedded in the signals. That is why well-designed pre-processing frameworks are crucial for cleaner signals and accurate models. In addition, some technological accidents may be encountered during the data collection phase. Power outages or battery failure may cause data loss.²²

Analyses of big data are possible with the support or cooperation of fields such as engineering or mathematics. This situation brings risks related to data security and patient privacy. For wearable technology

studies to be acceptable to patients, they must be conducted openly and protected.²² The United Kingdom's Department of Health and Social Care has published guidelines summarising and targeting key principles for safe and effective digital innovations. The Medicines and Healthcare Products Regulatory Agency has also published guidance for determining whether software and healthcare applications are medical devices.²⁶

Patient participation and the sustainability of the studies are also important. In a study conducted on clinically hospitalized adolescents at risk of suicide, patients reported that the most enjoyable part was participating, especially since it could help people with similar problems in the future;²⁷ however, more studies are needed to generalize this result.^{28,29} It is important for progress in this area to articulate how wearable devices are being adopted by users and how barriers to their widespread use are being addressed.³⁰

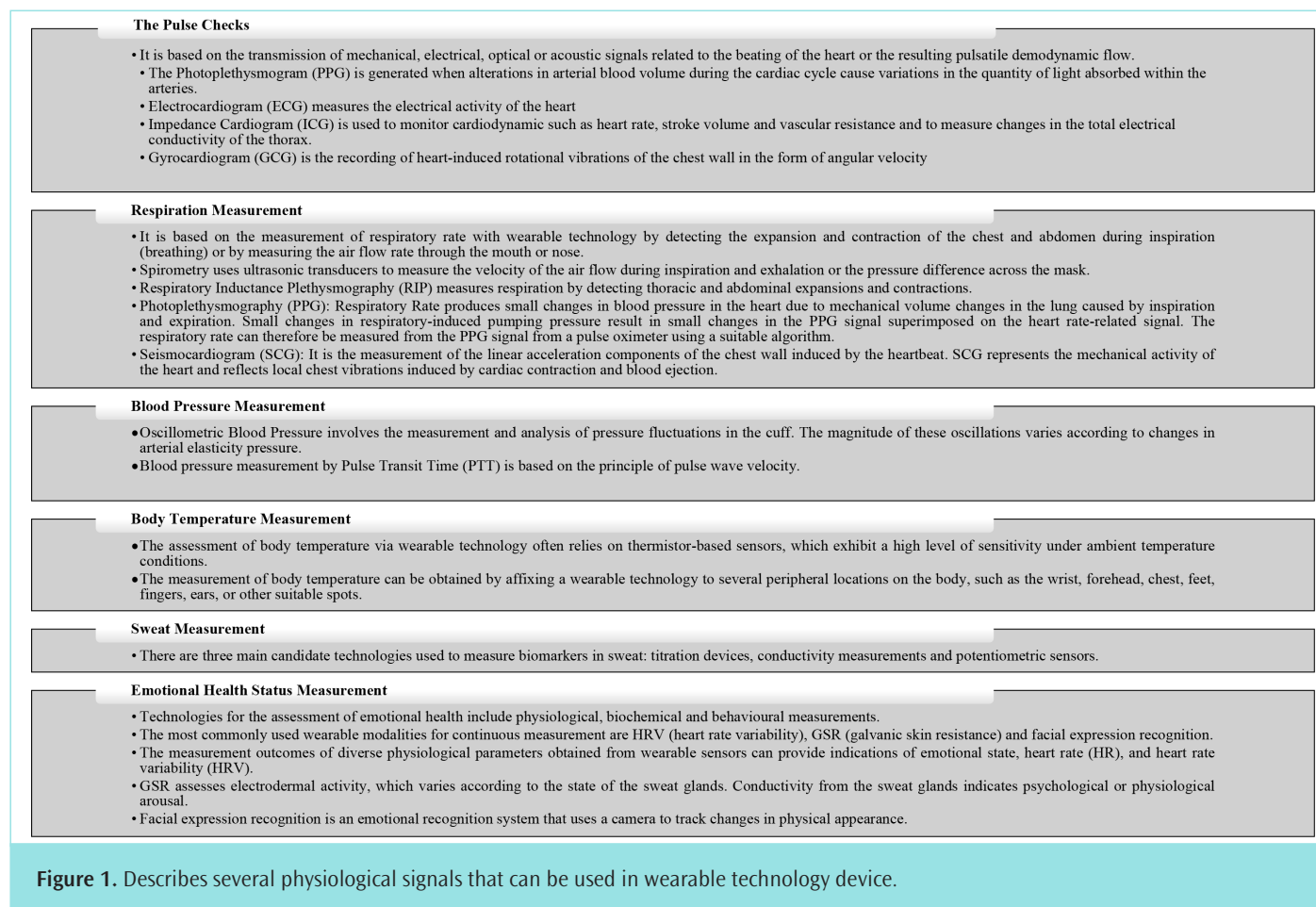
Wearable Technology and Mental Health

Mental illnesses are among the major causes of social and global disability.³¹ Serious mental illnesses affect many individuals worldwide, and disorders such as depression and anxiety lead to reduced productivity and economic losses.³² According to the global burden of disease reports, five of the twenty diseases in the burden of disease ranking are related to mental health issues.³³

Utilizing technological advancements in psychiatry is an essential issue, considering the disease and financial burdens. Recently, measurement-based care has been emphasized and recommended as a basis for improving the quality of mental health services.^{34,35} Wearable technology can improve patient outcomes through safely and objectively assessing patients with psychiatric disorders.³⁶ The use of digital tools in the field of psychiatry also benefits the dissemination of evidence-based practices. Evidence-based psychiatric care is not available in many parts of many developing and some developed countries. Inter-institutional reports related to the treatment compliance of patients with severe mental illness indicate that evidence-based treatment and care are applied in only 2% of cases.^{37,38} In this context, the utilization of wearable technology can provide valuable objective data and measurements that can significantly contribute to the field in terms of patient follow-up and therapy.

Robinson et al.³⁹ analyzed 12 articles in a systematic review of wearable technologies used in mental illnesses. It was determined that bioparameters such as electrodermal activity/galvanic skin resistance/skin conductance/skin temperature, physical activity, and heart rate (HR) were mostly evaluated with wearable technology, considering the results of the reviewed articles. Information on the monitoring of physiological parameters is provided in Figure 1.

Wearable technologies can also enable early recognition of risks of self-harm or harm to other persons by monitoring physiological or potential acute behavioral changes. One of these parameters is early recognition of the risk of self-harm through sleep monitoring. For example, sleep data can be assessed as a potential predictive factor for the risk of self-harm and used in preventative measures.⁴⁰ Studies have shown that too much or too little sleep can trigger, accelerate, and perpetuate depression.⁴¹ A study conducted with sensor-based sleep durations reported that sleep duration was effective in predicting suicidal ideation the next day, and this effect was similar to subjective sleep data.⁴² In another study conducted on undergraduate and graduate students, the



usefulness of wearable devices in predicting the severity of depression symptoms was examined. As a result of the study, it was reported that fluctuations in sleep efficiency can be measured with wearable devices, which may be associated with depression severity.⁴³

HR may be another method used to predict self-harm behavior. In a study of patients at risk of self-harm in an acute adolescent psychiatric clinic, Sheridan et al.⁴⁴ assessed patients' HRs for seven days with wearable technology devices, and self-harm risk with Columbia Suicide Severity Scores. An inverse correlation was found between the parasympathetic values measured in the study results and the risk of self-harm. The HR variable measured by wearable technology devices decreased in patients diagnosed with depression at the same time without an accompanying cardiovascular disease.⁴⁵⁻⁴⁷ Depression was inversely associated with physical activity measured from patients.^{48,49} A wearable device implanted in the skin may have acted as a biomarker for depression.^{50,51} HR is also one of the most effective methods for detecting and monitoring stress and anxiety in individuals.⁵²

According to the results of a study conducted with medical students, mobile mood monitoring with the help of wearable sensors was effective in predicting students' depression.⁵³ Changes in sleep patterns and physical activities assessed by wearable technology may give clues about depression and anxiety disorders.²⁴ In some mental disorders, there is a more pronounced sympathetic nervous system activation. This is similar to the fight or flight response to physical danger or mental

stress. This change can also be assessed with wearable technology, and used in the diagnostic phase of mental illnesses.²⁴

Real-time physiological parameters obtained through wearable technology can be used to improve traditional mental health interventions such as therapy or medication. It can also be used to guide the selection of the most appropriate treatment.^{54,55} These parameters involve using objective data in diagnosis and treatment selection. For example, Collier et al.⁵⁶ reported that the motion measurement technology used in the study helps clinicians with early diagnosis by assessing gait, balance, and postural kinematics. Objective and systematic data are important for developing and supporting evidence-based psychiatric practice in diagnosis and care provision. Wearable technology devices may also be useful in supporting interventions to improve cardiometabolic health in patients with schizophrenia. It is also reported that wearable devices support patient weight loss, and may be effective in improving lifestyle.⁵⁷

In addition to all these positive developments, Haines-Delmont et al.⁵⁸ used machine learning to analyze sensor and mobile data to assess the suicidal thoughts of patients discharged from a psychiatric hospital in the first week. The study results were reported as poor in terms of overall predictive accuracy.

CONCLUSION

Considering the historical problems in mental health services and the burden of disability, economic challenges, and care needs in mental illnesses, wearable technologies may promise hope for the development of mental health services. Simultaneous and objective monitoring of symptoms can contribute to evidence-based psychiatric care and positively affect patient care. However, most wearable technologies are still in the prototype stage. In a review of wearable technology in child and adolescent psychiatry, most of the studies are pilot studies, and randomized controlled studies are needed. The population in which wearable technology is applied, the generalizability of patient results, and patient feedback while using these devices will contribute to the shaping of these studies. Issues such as acceptance of the applied population, safety, ethics, privacy, and big data concerns in wearable technology need to be addressed to improve the availability and functionality of these devices for practical use.

Relevance Statement

Wearable technology provides us with objective data for monitoring and controlling existing risks. These objective data can help psychiatric nurses to make clinical decisions. It can help them recognize potential risks earlier and shape their care accordingly.

MAIN POINTS

- Considering the advancements of wearable technologies impact the mental health field, as they do in all other fields.
- Studies in this field and their results will be discussed, and current shortcomings and developments will be revealed.
- Wearable technologies in psychiatry will be evaluated through a strengths, weaknesses, opportunities, and threats (SWOT) analysis, highlighting their practice potential and ethical concerns. Wearable technologies in psychiatry will be evaluated through a SWOT analysis, highlighting their practice potential and ethical concerns.

Footnotes

Authorship Contributions

Concept: F.O., T.Ş.T., B.S., Design: F.O., T.Ş.T., B.S., Data Collection or Processing: F.O., T.Ş.T., B.S., Analysis and/or Interpretation: F.O., T.Ş.T., B.S., Literature Search: F.O., T.Ş.T., B.S., Writing: F.O., T.Ş.T., B.S.

DISCLOSURES

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Age-Related Volume Analysis of the Sella Turcica and Surgical Approach Metrics to the Pituitary Gland from Birth to Adulthood

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Abstract

BACKGROUND/AIMS: The pituitary gland is located in the sella turcica (ST). The volume change of the ST with age affects the pituitary gland. The volume of the ST and the distance from the points of surgical intervention to the pituitary gland should be known prior to surgery. Therefore, the aim of this study was to measure the age-related volumetric development of the ST and to determine the distances of the main surgical landmarks to the pituitary gland.

MATERIALS AND METHODS: Our study analyzed sagittal radiologic images of 794 individuals, aged 1-70 years. ST volumes and the distances for transsphenoidal, transcranial (TC), and frontoparietal (FP) surgical approaches were measured. ST volume was quantified using the Cavalieri principle on sagittal images, while surgical approach distances were determined using a ruler on the same sagittal radiological images.

RESULTS: The mean ST volume in the age range of 1-18 years was $259.32 \pm 38.28 \text{ mm}^3$, $262.40 \pm 38.74 \text{ mm}^3$ in males and $256 \pm 37.67 \text{ mm}^3$ in females. The volume increase in ST was observed at a high rate until adolescence, when bone development was the highest. There was no statistically significant difference in ST volume between genders. The mean lengths of the transsphenoidal, TC, and FP approaches were 81.64 ± 9.62 , 80.01 ± 14.85 and $92.56 \pm 8.54 \text{ mm}$, respectively.

CONCLUSION: Our study demonstrated that the volume of the ST increases continuously from birth to 18 years of age, with a marked acceleration after 14 years. Additionally, we quantified the distances from various surgical intervention points to the pituitary gland, providing essential data for optimizing surgical approaches.

Keywords: Sella turcica, volume, pituitary, surgery, radiology

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INTRODUCTION

Sella turcica (ST) is the anatomical structure known as the ST in the middle cranial cavity. It contains the pituitary gland. The name “ST” was given due to the anterior and posterior bony processes of the region observed in lateral head images and the resemblance of this depression to a Turkish saddle.¹ ST, which is easily observed on lateral radiographs, is located on the upper surface of the body of the sphenoid bone and consists of the hypophyseal fossa, tuberculum sellae anteriorly, and dorsum sellae posteriorly.

The morphological appearance of ST is established in early embryonic structures. The formation of both the pituitary gland and ST during the prenatal and postnatal periods is a complex process. These two significant structures are located in the boundary region, separating tissues of different origin and development. The pituitary fossa originates directly from the hypophyseal cartilage, which, in turn, is derived from the cranial neural crest cells of the early cartilaginous cranium. During the embryological development of humans, the ST area is the key point for the migration of neural crest cells to the frontonasal and maxillary developmental fields.^{2,3}

The development of this anatomically very important region in the prenatal and postnatal period has attracted the attention of scientists for many years due to its possible relationship with various anomalies, malformations and pathologies related to the calvaria and craniofacial region.⁴ During childhood and adolescence, the ST undergoes significant growth, corresponding with the overall growth of the skull and the development of the pituitary gland. This period is marked by hormonal surges, particularly during puberty, which necessitate changes in pituitary size and function. ST volume increases to accommodate these changes, and deviations from normal growth patterns can signal endocrine disorders.⁵

Neural, hormonal, vascular, osseous, and meningeal structures form a complex anatomy within the very narrow borders of the ST. The pituitary gland in the center fills 80% of the ST. The remaining area is filled by connective tissue and the perihypophyseal venous plexus.⁶⁻⁸

In the literature, changes in ST size and morphology are associated with many pathologies and syndromes.⁹⁻¹¹ Although most of these are chronic disorders that are not life-threatening in the short term, some may be associated with necrosis and/or adenomas of the pituitary gland that require rapid intervention.^{12,13} The pituitary gland, located in the pit surrounded by the dura mater, is prone to neoplastic transformation, and as a result, some well-known clinical syndromes occur.¹⁴ Apart from tumors, some diseases such as growth retardation, hypopituitarism, hyperthyroidism, and Williams syndrome are associated with a reduction in ST, whereas pathologies such as Cushing's disease, acromegaly, hypothyroidism, and anorexia nervosa are associated with an increase in ST volume.^{6,15}

Today, nearly all surgical interventions in this critical region use the transsphenoidal (TS) approach, except in special cases. The first TS procedure was performed on a cadaver in 1897.¹⁶ This approach has become the preferred method for sellar and parasellar surgeries, especially for pituitary adenomas, due to its ease, absence of scarring, no brain retraction, early patient mobilization, and shorter hospital stays.¹⁷⁻¹⁹ Success requires thorough knowledge of access routes, anatomy, and distances, with the surgical technique and instrument selection guided by preoperative radiologic examinations.^{20,21}

Understanding changes in the volume of the ST with age is essential for medical professionals, as it can provide insights into normal aging processes, help diagnose pathological conditions, and guide appropriate interventions. The morphology of the ST is important both in the evaluation of treatment outcomes, and late growth changes and in the assessment of cranial morphology.²² Measurements of the size of the ST as a function of age and information on the normal values of these measurements are insufficient. Changes in the size and morphology of the ST are particularly important for surgical interventions on the pituitary gland, and enlargement of this structure may create difficulties in terms of surgical access to the gland. This is particularly important in endoscopic TS pituitary surgery, where access to the pituitary gland may be impeded by an enlarged ST. Therefore, in our study, we aimed to measure the distances of surgical interventions to the pituitary gland, how these distances change with age, and how ST volume values change with age.

MATERIALS AND METHODS

Individuals

This study was conducted with the permission of Ordu University Scientific Research Evaluation and Ethics Committee (approval number: 2023/242, date: 29.09.2023). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study was performed retrospectively on sagittal computed tomography (CT) and/or magnetic resonance imaging (MRI) images of a total of 794 individuals aged 1-70 years, admitted to Ordu University Medical Faculty Education and Research Hospital. Retrospective analysis was performed on patients who were hospitalized between January 1st and July 1st, 2024. Individuals with any pituitary gland pathology or cranial deformity were excluded from the study. Therefore, radiological images that should have been excluded were analysed by the emergency medicine physician (Assoc. Prof. A. A., MD, PhD) involved in our study.

Acquisition of Computed Tomography and Magnetic Resonance Imaging Images

Cranial CT and MRI images (Canon Aquilion Lightning, Japan) of all individuals were obtained from Ordu University Training and Research Hospital and the Fonet PACS system. The volume measurements on the image were performed using the Cavalieri principle. The Cavalieri principle is based on counting the points on a dotted ruler placed on the structure to be measured.²³

Sella Turcica Volume Measurement

In this study, the Cavalieri principle was applied to CT images. The points falling on ST in the image were counted for each slice (Figure 1). Volume calculation was performed with the points obtained in each section as shown in the literature.^{24,25}

Transsphenoidal, Transcranial and Frontoparietal measurements

TS distance refers to the distance from the apex of the nose to the anterior wall of the ST. Transcranial (TC) length refers to the distance from the glabella or frons to the anterosuperior part of the ST. Frontoparietal (FP) distance refers to the distance from the bregma point to the upper wall of the ST (Figure 2). TC and FP intervention is a method used especially in cases where transnasal and/or TS interventions cannot be performed, such as during coronavirus disease-2019. Distance measurements were

performed on both CT and MRI. TS measurements were performed on 300 sagittal CT and 100 sagittal MRI images, and TC and FP measurements were performed on 200 sagittal CT and 72 sagittal MRI images.

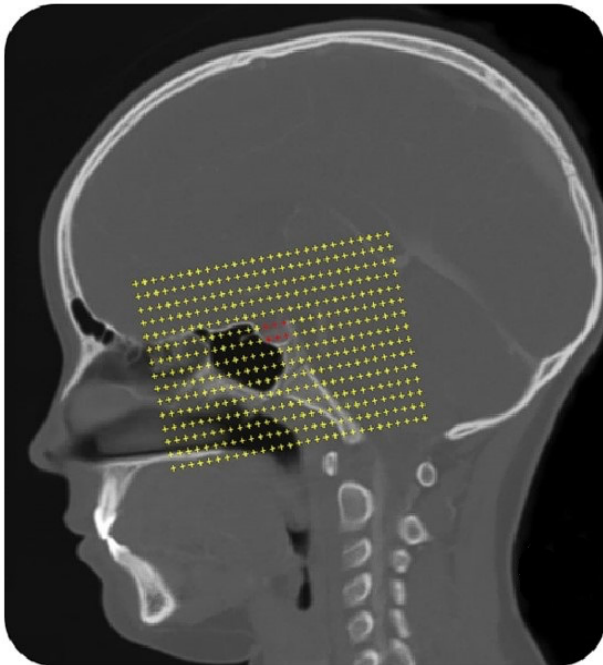


Figure 1. Image of a point ruler applied on the ST according to the Cavalieri principle (red dots represent the points on the ST).

ST: Sella turcica.

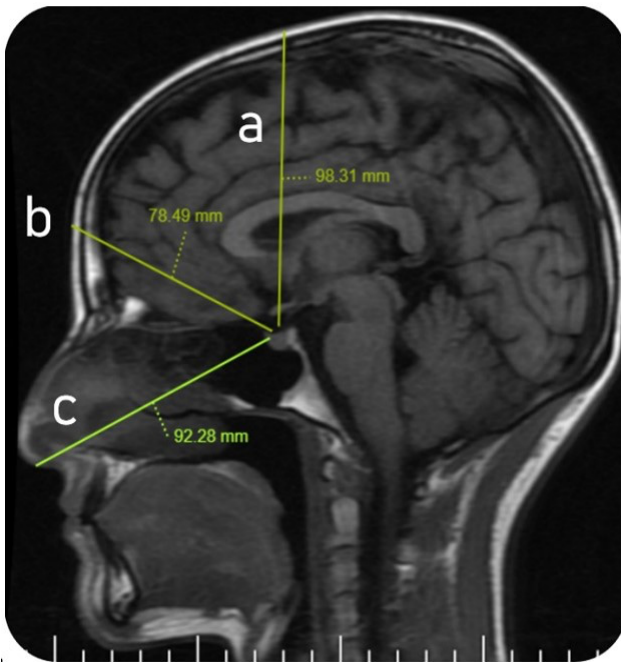


Figure 2. Measurement of frontoparietal (a), transcranial (b) and transsphenoidal (c) distance on the sagittal MRI image of an 18 years-old female.

MRI: Magnetic resonance imaging.

Statistical Analysis

Data were analyzed and distributed using SPSS v28. Normality of distribution was assessed using histogram, Skewness and Kurtosis, standard deviation (SD)/mean, and Kolmogorov-Smirnov test.²⁶ Normally distributed data are presented as mean \pm SD. The comparison of volume and length results between sexes was conducted using Independent samples t-tests. $p < 0.05$ was considered statistically significant.

RESULTS

Sella Turcica Volume Findings

ST volume measurements were performed on sagittal CT images of 394 individuals (197 males, 197 females) aged 1-18 years (11 males, 11 females in each age group). The age-related development of ST and its differences gender were determined. The data were plotted using software (GraphPad Prism 8.4.2, trial version).

The mean ST volume was $259.32 \pm 38.28 \text{ mm}^3$ in all individuals, $262.40 \pm 38.74 \text{ mm}^3$ in male subjects, and $256 \pm 37.67 \text{ mm}^3$ in female subjects. ST volume was compared between sexes, and no statistically significant difference was found ($p > 0.05$). The minimum (min.) ST volume was 157 mm^3 in female subjects aged 1 year and the maximum (max.) ST volume was 320 mm^3 in 18-year-old male subjects (Figure 3a). Although the volume increase in the ST is observed at a high rate until 10-11 years of age, when the development of bone and pituitary gland is the highest, the increase continues at a reduced rate at later ages (Figure 3b). However, the age-related increase in ST volume may vary from person to person.

Transsphenoidal, Transcranial and Frontoparietal Length Findings

In our study, TS length measurements were performed on 400 individuals (208 males, 192 females) aged between 1 and 70 years (19.70 ± 18.07). TC and FP length measurements were performed on 272 individuals (138 males, 134 females) aged between 1 and 70 years (23.54 ± 20.81). The mean lengths of TS, TC, and FP were 81.64 ± 9.62 (min.-max.: 52.21-102.85), 80.01 ± 14.85 (min.-max.: 43.64-106.48), and 92.56 ± 8.54 mm (min.-max.: 63.55-110.60), respectively (Figure 4). When the distribution of these lengths was analyzed according to gender, TS and FP values were found to be higher in males, and there was a statistically significant difference between genders ($p < 0.000$), whereas no difference was found in TC values.

When the changes according to age were examined, a high rate of increase occurred in the period from birth to puberty (1-20 years), when the highest development was observed, and then these increases stabilized in parallel with bone and organ development (Figure 5). According to these values, this rapid increase should be taken into consideration in surgical interventions performed on the pituitary gland in the period from birth to puberty.

As shown in Figure 4, FP length values were commonly found in a narrow range of 90-100 mm, but TC and TS values showed a wide spectrum of variability according to age. The reason for this may be the continuous development of the viscerocranium bones and the variation between individuals due to a combination of genetic, developmental, and environmental factors. Likewise, the growth of the brain and skull bones may occur at different rates in different individuals, leading to variations in TC and TS length.

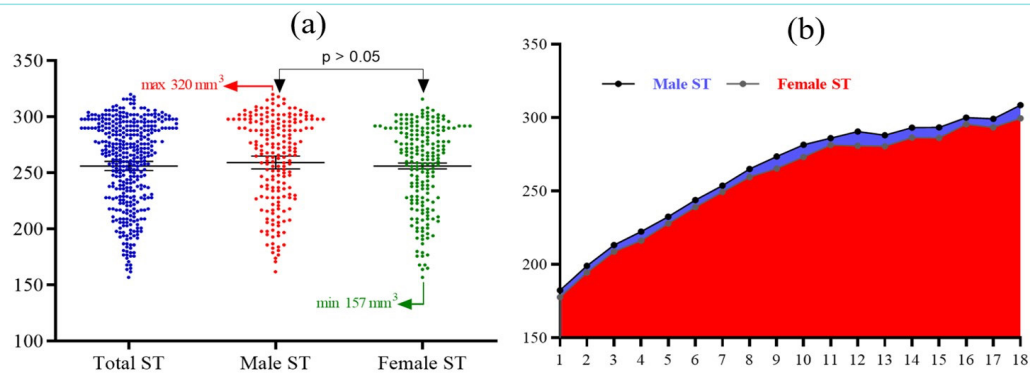


Figure 3. (a) distribution of ST volume in the whole population and by sex (x-axis: ST volume values, mm³), (b) development of ST volume according to age and sex (x-axis: ST volume values, mm³; y-axis: ages).

ST: Sella turcica.

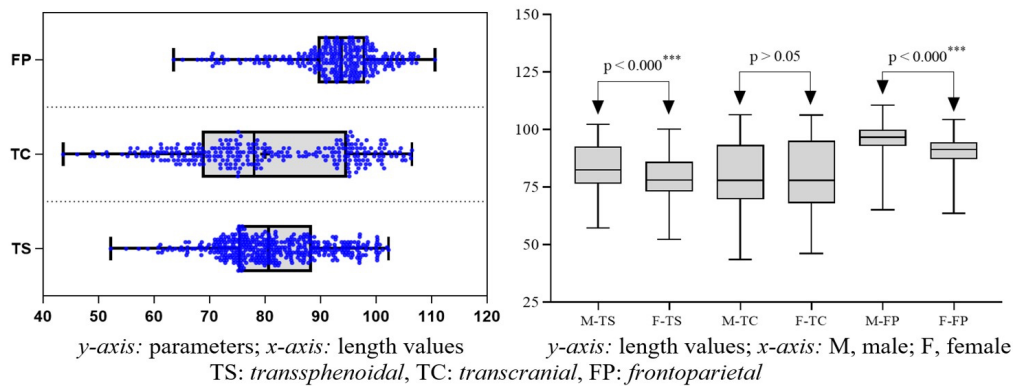


Figure 4. Descriptive statistics of TS, TC and FP lengths and distribution of these lengths according to gender.

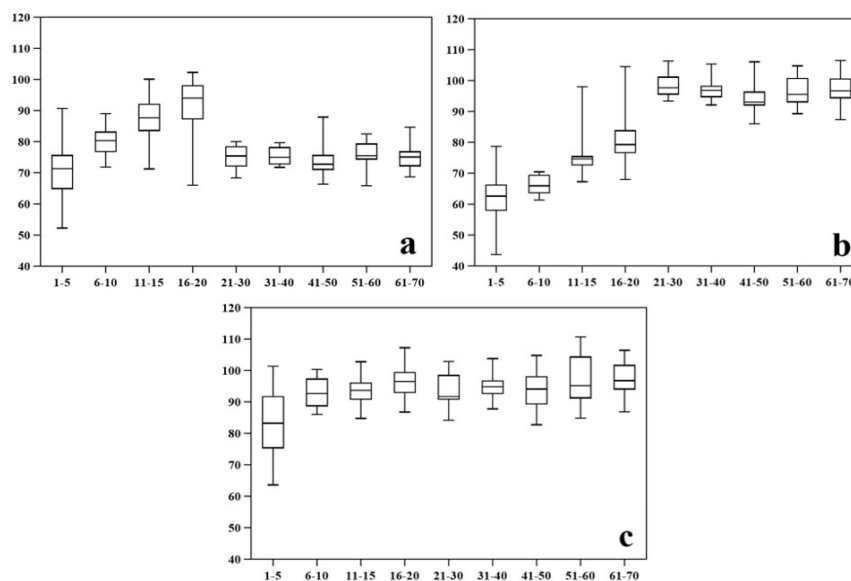


Figure 5. Distribution of TS (a), TC (b) and FP (c) lengths according to age (y-axis: length values; x-axis: age groups).

TS: Transsphenoidal, TC: Transcranial, FP: Frontoparietal.

DISCUSSION

Volume measurements of organs and structures in our body play a crucial role in diagnosing and monitoring many diseases. Therefore, determining normal organ parameters is essential for accurate evaluation and early diagnosis.²⁷ In our study, we calculated ST volume, which is associated with various pathologies, especially pituitary adenomas. ST volume can change throughout a person's life due to genetic, hormonal, and environmental factors.²⁸ We found no statistically significant effect of gender and age on ST volume. Volume values increase rapidly until puberty and then increase more slowly. This may be due to the rapid increase in bone development.

The ST, a saddle-shaped depression in the sphenoid bone, undergoes significant changes in size and morphology during growth. Studies have shown that ST increases in size after birth, with significantly higher volume values in males. The size of the ST changes according to gender and age, especially during adolescence.^{29,30}

Similar to our study, Axelsson et al.³¹ reported that the rapid increase in ST dimensions gradually slows down in the first years of life, increases again during puberty, and then grows at a low rate in late adolescence. Sathyanarayana et al.² found that ST volume was larger in males in their study but did not report a statistically significant gender difference.

During puberty, the pituitary gland usually enlarges, potentially increasing ST size. Clinically, changes in ST volume are important in diagnosing and treating pituitary disorders, craniofacial abnormalities, and some syndromes.^{11,32,33}

These changes in ST's size and morphology are particularly relevant for surgical interventions on the pituitary gland. An enlarged ST during

growth can pose challenges for surgical access to the gland. As ST size increases, it may encroach upon surrounding structures, complicating surgical interventions. This is especially important in endoscopic TS pituitary surgery, where access to the gland may be hindered by an enlarged ST.

Iskra et al.³³ reported that ST volume was 969.68 mm³ on CT images, 671.33 mm³ on cadavers, and 980.75 mm³ in European studies, in their meta-analysis on ST volume and morphology. Our results were lower than expected, likely due to age differences. Our study only reported ST volume development between 1-18 years. Although adult ST volume has been extensively analyzed, the volume development from birth to puberty is insufficiently studied.^{33,34}

The studies are close to each other, and the main reason for the volume differences is the change in the age range. In our study, postnatal development of ST was discussed. Pituitary gland interventions are common due to growth disorders in childhood. Therefore, the initial stage of postnatal development is particularly important. ST development is stabilized after the age of 20 according to studies. In many other studies, adult ST measurements were conducted, and therefore no difference is expected (Table 1).

The base of the ST is separated from the sphenoid sinus by a small bony plate. Therefore, the endoscopic TS approach is the most common and optimal method for surgical treatment of pituitary tumors.^{40,41} Although the length of TS has been discussed in many studies, information about its development and variation with age and gender is limited. Since it is the most common method for pituitary gland surgery, knowing the distance relevant to the procedure in all age groups is essential. In a study, the mean length from the columella to the anterior wall of the sphenoid sinus was reported to be 69.71±4.25 mm in individuals

Table 1. ST volume values in the literature

Research	Samples	Genders	Ages	Method	ST volumes
Our study	394 CT	197 males, 197 females	1-18	Cavalieri	259.32±38.28 mm ³ (total) 262.40±38.74 mm ³ (males) 256.00±37.67 mm ³ (females)
Iskra et al. ³³	18,364 radiographs	Not reported	Not reported	Meta-analysis	969.68±53.17 mm ³
Yamada et al. ³⁵	570 CT	Not reported	1-60	De Chiro-Nelson	Age 1=06±19 mm ³ Age 25=530±23 mm ³ 25+ ages =554±8 mm ³
Silveira et al. ³⁶	95 CBCT	35 males 60 females	16-57	Via software	920.01±163.26 mm ³
Chilton et al. ³⁷	960 radiographs	450 males-510 females	6-16	De Chiro-Nelson	6 years =196 mm ³ (males) 255 mm ³ (females) 16 years =549 mm ³ (males) 462 mm ³ (females)
Ortega-Balderas et al. ³⁸	173 CT	91 females, 82 males	53.2±17.6	De Chiro-Nelson	342.2±88.5 mm ³ (females) 378.6±113.9 mm ³ (males)
Taner et al. ³⁹	80 CBCT	40 males, 40 females	26.6±8.6 (females) 27.5±9.0 (males)	De Chiro-Nelson	1102±285.3 mm ³ (males) 951.3±278.5 mm ³ (females)
Venieratos et al. ⁴⁹	20 (dry skulls)	Not reported	Not reported	Via immersion	835 mm ³
Sherif et al. ⁵⁰	17 CT	All females	41±8	Via software	922±155 mm ³
Bakiri et al. ⁵¹	12 CT	All females	38.3±3.6	Via software	796±5.6 mm ³

ST: Sella turcica, CT: Computed tomography, CBCT: Cone beam computed tomography.

older than 15 years and 59.32 ± 7.80 mm in individuals younger than 15 years.⁴² In our study, we determined the mean length of the TS as 81.64 ± 9.62 mm and the mean length until puberty as 80.86 ± 8.97 mm. These results show that TS length increases rapidly from birth to puberty, then stabilizes.

Chumnanvej et al.⁴³ calculated the length from the columella to the sphenoid sinus on six cadavers and found a maximum length of 85.31 mm and a minimum length of 59.05 mm. Similarly, Baig et al.⁴⁴ found the mean distance from the nares to the posterior wall of the sphenoid sinus to be 83.82 mm. Although we measured the length from the columella to the anterior wall of the ST, our results are similar to those obtained in previous studies.

The TS approach is primarily preferred for sellar and parasellar tumors due to its low morbidity and mortality rates.⁴⁵ In some cases, resection via a TC approach may be required. TC surgery involves accessing the pituitary gland by making an incision in the anterior part of the skull over the frontal bone and retracting part of the brain. This approach is reserved for larger, more complex pituitary tumors that cannot be accessed via the TS route.^{46,47}

Less than 10% of pituitary adenomas require craniotomy. TC surgery is necessary in these cases despite its high mortality and morbidity rates. Therefore, knowing the TC distance is crucial for parasellar cavernous sinus and internal carotid artery surgery.⁴⁸

Study Limitations

Since the study is retrospective, the number of images is limited. There are no other limitations.

CONCLUSION

In conclusion, our study revealed differences in ST volume in the studied population and emphasized the importance of individualized surgical planning. Furthermore, precise measurement of the surgical pathways to the pituitary gland provides data necessary for optimizing surgical techniques and minimizing potential risks during procedures. This study paves the way for advances in surgical methodology, especially in the context of pituitary surgery.

MAIN POINTS

- Our study puts forward that the volume of the sella turcica (ST) increases continuously from birth to 18 years of age, with a marked acceleration after 14 years.
- This rapid increase should be taken into consideration in surgical interventions to be performed on the pituitary gland in the period from birth to puberty.
- There was no statistically significant difference in ST volume between the genders.
- Precise measurement of the surgical pathways to the pituitary gland provides data necessary for optimizing surgical techniques and minimizing potential risks during procedures.

ETHICS

Ethics Committee Approval: This study was conducted with the permission of Ordu University Scientific Research Evaluation and Ethics Committee (approval number: 2023/242, date: 29.09.2023)

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.D., A.T., Concept: M.D., İ.U., G.B.U., E.U., Design: M.D., T.E., S.Y., Data Collection and/or Processing: M.D., İ.U., G.B.U., A.A., Analysis and/or Interpretation: M.D., A.T., S.Y., Literature Search: M.D., T.E., Writing: M.D., İ.U., E.U.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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Maternal and Fetal Factors Affecting the Effectiveness of Vaginal Dinoprostone in Labor Induction

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Abstract

BACKGROUND/AIMS: Induction of labor is a common obstetric intervention used to encourage the onset of labor. The aim of the study was to evaluate the maternal and fetal factors that play a role in the efficacy of vaginal dinoprostone in labor induction.

MATERIALS AND METHODS: Our study included 780 patients who underwent pregnancy follow-up and delivery in our hospital between March 2018 and 2024. All data, including body mass index (BMI), age, parity, induction criteria, obstetric history, bishop score, time of delivery, newborn weight, and Apgar score, were entered by the delivery room physician. Data from 620 patients who had a successful delivery with vaginal dinoprostone application, and 160 patients who did not have a vaginal delivery were evaluated retrospectively.

RESULTS: The BMI value of women in group 2 at admission to the hospital was found to be significantly higher than that of women in group 1 ($p<0.001$). The Bishop score of women in group 1 at admission to the hospital was found to be significantly higher than that of women in group 2 ($p<0.001$). The nulliparity rate of women in group 2 was found to be significantly higher than that in group 1 ($p<0.001$). The uterocervical angle measurement of women in group 2 was found to be significantly lower than that in group 1 ($p<0.001$). The rate of newborns with 1st and 5th minute Apgar scores ≥ 8 in group 1 was found to be significantly higher than the rate in group 2 ($p=0.006$, $p=0.04$, respectively).

CONCLUSION: It was determined that parity was one of the important determinants in achieving vaginal delivery in pregnancies where dinoprostone vaginal insert was applied. It was determined that multiparous women benefited more from induction with dinoprostone. However, according to the results of our study, more research is needed to evaluate nulliparous pregnancies requiring induction.

Keywords: Dinoprostone, induction of labor, nulliparity, multiparity

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INTRODUCTION

Induction of labor (IOL) is a common obstetric intervention that uses artificial methods to stimulate the onset of labor by artificially initiating the process of cervical effacement, cervical dilation, and uterine contractions.¹ IOL is often considered when prolonged pregnancy poses a risk of death or morbidity for the mother or child or upon the request of pregnant women at term.² IOL is considered indicated when outcomes for the fetus, the mother, or both are better than expectant management, which means waiting for spontaneous onset of labor.³ It is an increasingly common practice in modern obstetrics to provide better care for both the fetus and the mother.⁴ For example, the rate of IOL more than doubled in 2006, reaching 22.5% of all births in the USA.⁴ The American College of Obstetricians and Gynecologists (ACOG) has a comprehensive list of recommendations for the timing of delivery, including some of the common clinical scenarios listed for this purpose.⁵ Also, ACOG recently endorsed elective IOL as a “reasonable” option following the publication of results from the Animal Research: Reporting of *In Vivo* Experiments (ARRIVE) (randomized trial of induction versus expectant management) study conducted by the Eunice Kennedy Shriver National Institute.⁶ However, the Society for Maternal-Fetal Medicine statement suggested that inducing labor at 39 weeks’ gestation in low-risk nulliparous women provides maternal benefits without an increase in adverse neonatal effects.⁷ The New England Journal of Medicine published the ARRIVE study, which compared cesarean section (C/S) rates and perinatal outcomes in nulliparous pregnant women who underwent elective IOL at 39 weeks of gestation with expectant management. The results showed a significantly lower C/S rate in the induction group and no statistically significant difference in the incidence of adverse perinatal outcomes.⁸ Another published study found that the likelihood of a C/S was reduced in nulliparous and multiparous women who were electively induced between 37 and 40 weeks of pregnancy.⁹ It also found that women were not at increased risk of third or fourth degree tears or having an operative vaginal delivery, regardless of gestational age.⁹ However, a Cochrane systematic review also showed that IOL is beneficial because it is associated with fewer perinatal deaths, and improved birth outcomes in women after delivery.¹⁰ Cervical ripening is an important precursor to successful labor induction and is accompanied by adequate and strong uterine contractions at regular frequency.¹¹ There are two main options for cervical ripening: namely, mechanical and pharmacological methods.¹²⁻¹⁶ Oxytocin may be one of the most popular pharmacologic agents for labor induction; however, it has minimal effects on cervical ripening.¹⁷ Prostaglandin analogs, including dinoprostone, a synthetic preparation chemically identical to naturally occurring PGE₂, and misoprostol, a synthetic PGE₁ analog, not only have an effect on cervical ripening but also play an important role in the IOL.^{18,19} Due to its benefits such as low price and easy storage (no refrigeration required), misoprostol may be the most commonly used pharmacological agent for labor induction worldwide.²⁰ However, Misoprostol is not licensed for labor induction, and has been widely used off-label (via oral or vaginal administration) worldwide for many years.²¹ In contrast, a slow-release vaginal product used for dinoprostone administration contains 10 mg of dinoprostone dispersed throughout the matrix of a thin flat polymeric hydrogel drug delivery device designed to provide a controlled and constant release of dinoprostone from the reservoir at 0.3 mg/hr. The efficacy profile is faster and more variable in women without membrane rupture than in women with membrane rupture.²² The main advantage of the dinoprostone slow-release vaginal insert is

enabling rapid retrieval in the event of uterine tachysystole or abnormal fetal heart rate monitoring, and has a low side effect profile.²³ Our study aimed to evaluate the maternal and fetal factors that play a role in the effectiveness of vaginal dinoprostone in labor induction.

MATERIALS AND METHODS

The present study was conducted as a retrospective observational following the Principles of the Helsinki Declaration. Consent forms were obtained from all patients. The study received approval from Buca Seyfi Demirsoy Training and Research Hospital hospital’s Ethics Committee (approval number: 2024/308, date: 26.06.2024). Our study included 780 patients whose pregnancy follow-ups and deliveries were performed in our hospital between March 2018 and 2024 a more recent past date. Data from 620 patients who had a successful delivery with vaginal dinoprostone application and 160 patients who could not have a vaginal delivery were evaluated retrospectively. Inclusion criteria were singleton pregnancy, vertex presentation, >36 weeks of gestation, Bishop score <7, absence of labor signs, and reassuring fetal heart rate. Gestational age was calculated using Naegele’s rule and confirmed by early pregnancy ultrasound.²⁴ Exclusion criteria included abnormal placentation, antepartum bleeding, fetal malformation, history of C/S or uterine surgery, and other contraindications to vaginal delivery. Cervical dilatation, cervical effacement, cervical consistency, cervical position, and station of fetal presenting part were evaluated in calculating the Bishop score.²⁵ The American Diabetes Association Criteria were used to diagnose gestational diabetes mellitus (GDM).²⁶ GDM was diagnosed if fasting blood glucose was above any of the following criteria: 92 mg/dL; 1 hour: 180 mg/dL; 2 hours: 153 mg/dL. In pregnant women who have not previously been diagnosed with diabetes mellitus, a 75-g oral glucose tolerance test (OGTT) test is performed at 24-28 weeks, and plasma glucose is measured during fasting, 1st and 2nd hours. It is appropriate to perform OGTT in the morning after an overnight fast of at least 8 hours.²⁶ The American Diabetes Association Criteria were used to diagnose type-2 diabetes mellitus.²⁶ Diabetes is diagnosed if HbA1C is greater than or equal to 6.5%, fasting blood glucose is greater than or equal to 126 mg/dL, or two-hour blood glucose is >200 mg/dL.²⁶ Pregnancy-induced hypertension (PIH) was diagnosed in accordance with the most recent ACOG bulletin.²⁷ The combination of hypertension and proteinuria is used for the diagnosis of preeclampsia. Hypertension is defined as blood pressure levels of at least 140 mmHg for systolic or at least 90 mmHg for diastolic in measurements taken four hours or longer after the 20th week of pregnancy in a woman whose blood pressure values were previously normal. Severe hypertension is considered when blood pressure is at least 160 mmHg systolic or at least 110 mmHg diastolic. To diagnose preeclampsia, women with hypertension also require the presence of proteinuria, defined as at least 300 mg in a 24-hour urine collection. PIH is diagnosed in patients who meet hypertension criteria for preeclampsia without proteinuria or serious additional problems.²⁷ amniotic fluid index ≤5 is considered one of the most important criteria in the ultrasonographic diagnosis of oligohydramnios.²⁸ Routine fetal heart monitoring was performed for 2 hours, and treatment with the dinoprostone vaginal slow-release system (Propess®, Ferring, Controlled Therapeutics Ltd, UK) was started after the fetal heart rate was observed to be normal. Posterior fornix dinoprostone placement was performed and maintained for a maximum of 12 hours in pregnant women without contraindications, according to the manufacturer’s instructions. All participants underwent continuous fetal monitoring. According to the modified protocol per

the manufacturer's recommendation, dinoprostone was removed in the presence of uterine tachysystole (defined as more than five contractions in 10 minutes in a 30-minute period), non-reassuring fetal heart rate, other non-specific adverse events (intolerable painful uterine contractions), persistence in the vagina for >12 hours, and spontaneous rupture of membranes. If regular uterine contractions were not noted 1 hour after removal of dinoprostone, intravenous oxytocin was additionally used to continue induction. All data, including BMI, age, parity, induction criteria, obstetric history, bishop score, reason for vaginal dinoprostone removal, time of delivery, neonatal weight, and Apgar score, were entered by the delivery room physician. The delivery room fetal monitoring device provided continuous close observation of fetal heart rate and uterine contraction patterns. Women with successful labor induction were divided into group 1, and those with unsuccessful labor induction into group 2.

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 (IBM-Inc.-Chicago-USA). The normality of the distribution was evaluated with the Kolmogorov-Smirnov test. Parameters that were not normally distributed were analyzed with the Mann-Whitney U test. Chi-square tests and Fisher's exact test were used in the analysis of categorical data. Parameters that were not normally distributed were presented as median (minimum-maximum). Number and percentage (%) were used to represent qualitative data. Results were evaluated at a 95% confidence interval. The p-value considered statistically significant was <0.05.

RESULTS

In our study, the mean age of the women in group 2 was found to be significantly higher than that of women in group 1 ($p=0.001$). The Bishop score at admission of women in group 1 was found to be significantly higher than that of women in group 2 ($p<0.001$). BMI scores of women in group 2 were found to be significantly higher than those of women in group 1 ($p<0.001$). The nulliparity rate of women in group 2 was found to be significantly higher than that of women in group 1 ($p<0.001$). The uterocervical angle measurement of women in group 2 was found to be significantly lower than that of women in group 1 ($p<0.001$). The time to delivery after insertion in group 2 women was found to be significantly higher than in group 1 women ($p<0.001$). The time to delivery after retrieval in the group 2 women was found to be significantly higher than in the group 1 women ($p<0.001$) (Table 1).

The rate of women with a 1-minute Apgar score ≥ 8 in group 1 was found to be significantly higher than that of women in group 2 ($p=0.006$). The rate of women with a 5-minute Apgar score ≥ 8 in group 1 was found to be significantly higher than that of women in group 2 ($p=0.04$), (Table 2).

DISCUSSION

The main purpose of the IOL is to ensure timely cervical ripening and successful vaginal birth. In our study, 79.4% of term pregnancies treated with dinoprostone slow-release vaginal insert for IOL had a successful vaginal delivery. This success rate was consistent with many other previous studies, with a successful vaginal delivery rate ranging from approximately 70% to 90% after using a dinoprostone slow-release vaginal insert for the IOL.²⁹⁻³⁴ In the 2008 report of the Turkey Demographic and Health Survey (TDHS), the C/S rate was found to be 37%, and in the TDHS-2013 report, it was 48%.³⁵⁻³⁷ These rates are significantly higher than the 15% rate given as an acceptable cesarean

delivery rate by the World Health Organization.³⁸ In light of this information, the birth rate data in our study reveal that dinoprostone administration is an effective method for successful initiation of labor.

In our study, we demonstrated that parity is one of the most important determinants in achieving successful vaginal delivery in term pregnancies treated with dinoprostone slow-release vaginal insert for IOL. 96.7% of all multiparous women had a successful vaginal delivery, and in the nulliparous group, the rate of successful vaginal delivery after dinoprostone slow-release vaginal insert treatment, was determined to be 70.2%. However, there are different results in the literature regarding the success rates of deliveries after dinoprostone application in multiparous and nulliparous pregnant women.^{39,40} In a

Table 1. Demographic and clinical characteristics of the groups

Variables	Group 1 n=620 79.4%	Group 2 n=160 20.6%	p-value
Maternal age (years)	30 (23-43)	31 (25-40)	0.001
Gestational age (weeks)	40 (38-41)	40 (38-41)	0.9
Bishop score at admission (n)	3 (1-4)	2 (1-4)	<0.001
Body mass index (kg/m ²)	28 (25-31)	30 (26-34)	<0.001
Parity			
Nulliparity	357 (57.6%)	151 (94.4%)	<0.001
Multiparity	263 (42.4%)	9 (5.6%)	
Indications for induction			
Elective	480 (77.4%)	113 (70.6%)	0.2
Oligohydramnios	24 (3.9%)	5 (3.1%)	
Gestational diabetes mellitus	49 (7.9%)	15 (9.4%)	
Type 2 diabetes mellitus	9 (1.5%)	5 (3.1%)	
Pregnancy induced hypertension	58 (9.4%)	22 (13.8%)	
Use of painless anesthesia	515 (83.2%)	141 (88.1%)	0.1
Uterocervical angle (°)	100 (60-140)	90 (60-130)	<0.001
Time to delivery after insertion (hours)	18 (7-29)	32 (21-45)	<0.001
Time to delivery after retrieval (hours)	11 (4-21)	14.5 (10-29)	<0.001

*Values are expressed as frequency or percentage. Values are expressed as median (minimum-maximum). The Mann-Whitney U test was conducted. The Chi-square test and Fisher's exact test were used.

Table 2. Fetal outcomes between the groups

Variables	Group 1 n=620 79.4%	Group 2 n=160 20.6%	p-value
Fetal weight (grams)	3,180 (2,340-4,310)	3,165 (2,330-4,290)	0.9
Apgar score (1-minute)			
≤7	180 (29%)	65 (40.6%)	0.006
≥8	440 (71%)	95 (59.4%)	
Apgar score (5-minute)			
≤7	18 (2.9%)	10 (6.3%)	0.04
≥8	602 (97.1%)	150 (93.8%)	

*Values are expressed as frequency or percentage. Values are expressed as median (minimum-maximum). The Mann-Whitney U test was used. Chi-square test and Fisher's exact test were used.

retrospective study by Zhao et al.⁴¹, results revealed that parity was the strongest predictor of successful vaginal delivery in term pregnancies when comparing the efficacy of dinoprostone slow-release vaginal insert between multiparous and nulliparous women. In the study by Huang et al.⁴², parity was proven to be the main factor contributing to the time to vaginal delivery. A significant decrease in this time was observed in multiparous women compared to nulliparous women.

In the present study, the mean age was found to be significantly higher in the unsuccessful vaginal delivery group. In the study conducted by Pevzner et al.⁴³, it was revealed that a maternal age of <35 years significantly supports successful labor induction. Similarly, in the study conducted by Obut et al.⁴⁴, it was revealed that increasing maternal age reduces the probability of vaginal delivery. In the present study, no statistically significant relationship was found between gestational age, birth weight, IOL indication, and use of painless anesthesia parameters and successful vaginal delivery. Possible reasons could be the small sample size, as a limited sample size may prevent less important factors from reaching statistical significance. Only the most significant factor can be repeated in almost all studies.

In the literature, labor induction is shown to be more likely to be successful in women with lower BMI.^{45,46} In our study, similar to the literature, BMI was found to be significantly lower in pregnant women who had successful vaginal births.

Higher bishop scores have traditionally been associated with higher vaginal birth success rates.^{47,48} However, there are studies that question the reliability of Bishop scores in predicting birth outcomes.^{49,50} In our study, bishop scores were found to be significantly higher in patients who had a successful vaginal delivery with vaginal dinoprostone administration, as supported by the results obtained in most randomized trials and clinical guidelines for labor induction.^{51,52}

In our study, the 1st- and 5th-minute Apgar scores of patients who had a successful vaginal delivery were found to be significantly higher. In the literature, neonatal outcomes were found to be positive in pregnancies induced with dinoprostone.^{41,53}

In our study, time to delivery after insertion (hours) and time to delivery after retrieval (hours) were found to be significantly lower in patients who had a successful vaginal delivery compared to patients who did not have a vaginal delivery. Similarly, in the literature, the time to delivery after insertion (hours) and time to delivery after retrieval (hours) were found to be lower in patients who had a successful delivery with dinoprostone compared to patients who underwent spontaneous delivery follow-up or C/S due to induction failure.

Whether epidural analgesia increases the risk of cesarean delivery and prolongs labor has been intensely debated during the last decade.⁵⁴ Unfortunately, good studies are few and most have had small sample sizes. Epidural analgesia was associated with slow progress of labor, which increased the rate of instrumental delivery. However, in our study, no relationship was found between the use of painless anesthesia and the success of vaginal delivery.

In our study, uterocervical angle measurement was found to be significantly higher in patients who had successful vaginal delivery compared to patients who did not have a vaginal delivery. However, in the study conducted by Ileri et al.⁵⁵, no relationship was found between uterocervical angle and delivery success in pregnancies induced with

dinoprostone. In the study conducted by Yang et al.⁵⁶, it was stated that the use of uterocervical angle measurement and bishop score could together help predict the success of labor induction. In another study in the literature, it was stated that the uterocervical angle could be used, in addition to cervical length measurement, to assess the risk of premature birth and term pregnancy when predicting delivery success.⁵⁷

Our study showed that the success rate of vaginal delivery in nulliparous term pregnancies was only 70.2%, suggesting that other strategies may be considered instead of the dinoprostone slow-release vaginal insert for IOL for this group. In fact, many studies have supported the use of PGE1, and some have suggested the combination of mechanical and pharmacological methods or the use of mechanical or pharmacological agents alone, compared with PGE2.⁵⁸ A randomized controlled trial by Edwards et al.⁵⁹ compared the combined use of a dinoprostone slow-release vaginal insert and a Foley catheter with the use of a Foley catheter alone for cervical ripening and labor induction. This study supported the combined use of a dinoprostone slow-release vaginal insert and a Foley catheter for cervical ripening over the use of a foley catheter alone for IOL in nulliparous term pregnant women. The results showed that the combination strategy could shorten the time to vaginal delivery in nulliparous women but not in multiparous women.

Study Limitations

Our current study did not provide any recommendations on this issue due to its single-arm nature. The limitation of study is that it is retrospective in nature and a single-arm study.

CONCLUSION

Since multiparous women benefit the most from IOL using the dinoprostone slow-release vaginal insert, the two combinations mentioned above may be considered. However, based on the results of the current study, further research is needed to evaluate nulliparous term pregnancies requiring IOL.

MAIN POINTS

- The success rates of vaginal delivery after induction of labor (IOL) with dinoprostone in nulliparous term pregnancies are not satisfactory.
- In nulliparous term pregnancies, other strategies may be considered instead of dinoprostone slow-release vaginal insert for IOL.
- Multiparous women benefit the most from IOL using dinoprostone slow-release vaginal insert.

ETHICS

Ethics Committee Approval: The study received approval from Buca Seyfi Demirsoy Training and Research Hospital hospital's Ethics Committee (approval number: 2024/308, date: 26.06.2024).

Informed Consent: Consent forms were obtained from all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: U.A., F.E., Concept: O.Y., C.A., Design: H.A.A., B.E., Data Collection and/or Processing: S.E., T.B.B., Analysis and/or Interpretation: H.A.A., C.A., Literature Search: U.A., S.E., B.E., Writing: O.Y., C.A., T.B.B., F.E.

DISCLOSURES

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Assessment of Herbal Interactions with Anti-Cancer Drugs Using Two Drug Interaction Checker Databases and Attitudes of Cancer Patients Toward the Use of Herbal Products/Medicines: Single Center Experience

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Abstract

BACKGROUND/AIMS: Cancer patients can use herbal medicines/products to reduce symptoms and side effects, prevent metastasis and strengthen their immune system during the chemotherapy cycle. The first purpose of the study was to evaluate the attitudes of cancer patients toward the use of herbal medicines/products and to determine the herbal medicines/products used by cancer patients. The second purpose of the study was to determine the interactions between herbal medicines/products and anti-cancer drugs, using the Drugs.com and Medscape.com databases in the Oncology Clinic of Near East University Hospital.

MATERIALS AND METHODS: This was a retrospective and cross-sectional study conducted with cancer patients receiving chemotherapy in the Oncology Clinic at Near East University Hospital, between 1 June 2022 and 30 July 2022.

RESULTS: Only fifty-five cancer patients agreed to participate in this study. The highest score of 2.22 ± 0.98 was for herbal medicines/products that strengthen the immune system and the lowest score of 1.15 ± 0.45 was for herbal medicines/products that are better than chemotherapy. According to the Medscape.com database one interaction between *Eucalyptus* + and fluorouracil was in the “monitor closely” category. On the other hand, according to the Drugs.com database, two interactions between docetaxel + *Echinacea* and cyclophosphamide + *Echinacea* were categorized as moderate interactions.

CONCLUSION: This study showed that cancer patients' attitudes toward herbal product use were poor. Cancer patients with poor attitudes toward treatment were found to use more herbal products than cancer patients with good attitudes.

Keywords: Cancer patients, complementary and alternative medicine, drug-herbal interactions, herbal products

INTRODUCTION

Regarding the Global Cancer Observatory, an estimated 18.1 million new cases and 10 million deaths from all cancers combined occurred worldwide in 2020. It is also estimated that by 2040, 28 million new cases

of cancer will occur worldwide each year.¹ According to the National Cancer Institute, complementary and alternative medicine (CAM) is a medical term that refers to practices used to help manage the side effects of cancer treatments, as well as to try to treat or cure cancer diseases, that are not part of standard medical care.² The reasons for the current

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popularity of CAM, which is used by 25-50% of the general population in industrialised countries, are known to be complicated. There may be complex social and cultural reasons underlying this popularity.³⁻⁵ CAM treatments include botanical and nutritional products such as herbal, dietary, and vitamin supplements. These products are not required to be approved by the Food and Drug Administration before being dispensed to the public. Moreover, patients can obtain these products without a prescription. The administration of herbal medicines in combination with other medications or in high doses may be harmful.² Previous studies have shown that cancer patients utilise herbal products before, during, and after cancer treatment.⁶⁻⁹ Grapefruit juice, St John's Wort, Ginkgo, and Kava Kava, interact with cancer drugs and may alter the effectiveness or toxicity of the drugs due to herb-drug interactions. Many cancer patients, especially geriatric patients, are at risk of polypharmacy due to the number and variety of chemotherapy drugs and other medications. Furthermore, combining herbal products with chemotherapy may increase the risk of food-drug interactions.¹⁰⁻¹³ This may lead to a decrease in the quality of life, a change in the treatment protocol, or an increase in health costs in the treatment of cancer patients.¹⁴ Therefore, the study aimed to assess the attitudes of cancer patients receiving chemotherapy towards the use of herbal products. It also evaluated the possible drug interactions between herbal products and chemotherapy drugs using two drug interaction checker databases at the Oncology Clinic of Near East University Hospital.

MATERIALS AND METHODS

This was a retrospective and cross-sectional study conducted with cancer patients receiving chemotherapy at the Oncology Clinic of Near East University Hospital, North Cyprus between 1 June 2022 and 30 July 2022. The first purpose of the study was to assess the attitudes of cancer patients toward the use of herbal products and the herbal products used by cancer patients. The second purpose of the study was to assess the interactions between herbal medicines/products and anti-cancer drugs by consulting Drugs.com and Medscape.com databases in the Oncology Clinic of Near East University Hospital University Hospital.

The study population consisted of all adult cancer patients who received outpatient treatment at the Near East University Hospital during the data collection period and met the inclusion criteria. Cancer patients who received chemotherapy and were older than 18 years were included in the study. Patients who had not received chemotherapy or who did not want to participate were excluded from the study. All participants were informed about the aim of the study and provided verbal consent to the researchers before participating. The Institutional Review Board of Near East University approved this study (approval number: 2022/102, date: 28.04.2022).

Questionnaire

The questionnaire used in the study consisted of three parts. The first part consisted of five questions evaluating the demographic information of the participants. The second part consisted of eight questions evaluating the attitudes of cancer patients towards the use of herbal products with a 3-point Likert scale (agree, disagree, neutral). The questionnaire was formed by making modifications to a questionnaire used in a previous study.¹⁴ The questionnaire was prepared by an expert panel consisting of one pharmacologist, two clinical pharmacists, and one pharmacognosist. This questionnaire was sent to two oncology

pharmacists for face validity of the questionnaire. According to the attitude scale, cancer patients who scored 15 or more had a good attitude (out of 24) and those who scored lower than 15 had a poor attitude. The third part consisted of two questions about the names of the herbal products and the chemotherapy drugs used by the cancer patients. The questionnaire was used in both Turkish and English. Also, the questionnaire was translated into Turkish using a forward and backward method.

Drug and Herbal Interaction Evaluation

Drugs.com and Medscape.com drug interaction checker databases were used to determine the interactions between herbal products and chemotherapy drugs. Mechanisms of drug-drug interaction were categorized as pharmacodynamic, pharmacokinetic, and unknown mechanism of action. According to Medscape.com, interactions are divided into four categories: minor, monitor, serious-use alternative, and contraindicated. Additionally, according to Drugs.com, interactions are divided into 4 categories: minor, moderate, major, and unknown.

Statistical Analysis

This study's data were evaluated using the Statistical Package for Social Sciences version 21. A p-value of less than 0.05 was considered statistically significant. Demographic information and data on cancer patients' attitudes are shown in percentages and frequencies. This study determined the relationship between social-demographic factors and cancer patients' attitudes towards herbal product use, and between cancer patients' attitudes and herbal product users, by applying the chi-square test. Internal consistency was determined by Cronbach's alpha.

RESULTS

Between 1 June 2022 and 30 July 2022, a total of fifty-nine cancer patients applied to the oncology clinic. Fifty-five cancer patients consented to the study, while only four cancer patients declined. 65.5% of cancer patients were female and 34.5% were male. 50.9% of cancer patients were less than sixty-five years old and 49.1% were older than sixty-five. 58.2% of cancer patients lived in a city and 41.8% lived in a village. The most common cancer type was breast cancer (30.9%) (Table 1).

The highest score of 2.22 ± 0.98 was for the item that herbal medicines/products strengthen the immune system, and the lowest score of 1.15 ± 0.45 was for herbal medicines/products that are better than chemotherapy. A Cronbach's alpha coefficient of (0.65) was calculated for the cancer patients' attitudes (Table 2).

There was no statistically significant association between demographic factors and cancer patients' attitude towards using herbal products (Table 3).

There was no statistically significant association between the attitudes of herbal product users and those of cancer patients towards the use of herbal products (Table 4).

Cancer patients used twenty-four types of herbal products/medicines. The use of herbal products per patient was 0.43 on average. In cancer patients, the most frequently used herbal medicine/product was Cinnamon tea (8 patients, 14.54%; *Cinnamomum cassia* Blume and *Cinnamomum verum* J. Presl) (Table 5).

Table 1. Demographic characteristics of cancer patients

	n (%)
Gender	
Female	36 (65.5%)
Male	19 (34.5%)
Age (mean \pm SD)	
<65 years	28 (50.9%)
\geq 65 years	27 (49.1%)
Highest education status	
Primary school	11 (20%)
High school	23 (41.8%)
University	21 (38.2%)
Living place	
City	32 (58.2%)
Village	23 (41.8%)
Cancer types	
Breast cancer	17 (30.9%)
Lung cancer	6 (10.9%)
Gastrointestinal cancer	15 (27.3%)
Gynaecology cancer	6 (10.9%)
Others	11 (20%)
Attitude level	
Poor	36 (65.5%)
Good	19 (34.5%)
Herbal use	
Use	31 (56.4%)
Don't use	24 (43.6%)

SD: Standard deviation.

In this study, herbal medicines/products and drug interactions were checked using the Drugs.com and Medscape.com databases (Table 6). The term not available (N/A) was added for herbal medicines/products not found in Drugs.com, and Medscape.com databases.

DISCUSSION

The use of herbal products and anti-cancer drugs together may cause unexpected side effects. Therefore, it is of great importance that the use of herbal products is determined by healthcare professionals. If an interaction is detected between an herbal product and anti-cancer drugs, patients should be educated by oncology pharmacists and physicians about possible side effects and the potential need to stop using the herbal product during chemotherapy. This study determined that cancer patients have negative attitudes about the use of herbal products. However, the use of herbal products was higher in cancer patients with poor attitudes than with good attitudes.

According to the Medscape.com database, one interaction between *Eucalyptus* and fluorouracil was determined to be in the monitor closely category. The Medscape.com database reported that *Eucalyptus* increases the levels of fluorouracil. On the other hand, *Eucalyptus* is N/A in the Drugs.com database, meaning that the oncology pharmacist did not evaluate the interaction between *Eucalyptus* and fluorouracil using this database. According to the Drugs.com database, two interactions between docetaxel + *Echinacea* and cyclophosphamide + *Echinacea* were in the moderate interaction category. The Drugs.com database reports that *Echinacea* may alter blood levels and effects of docetaxel and cyclophosphamide. On the other hand, according to the Medscape.com database, no interaction was found between *Echinacea* and chemotherapy agents. It is of great importance that herbal medicines/products, N/A in databases, used by cancer patients are considered and investigated. Furthermore, oncologists and oncology pharmacists should determine the frequency and dosage of herbal products. If they detect an interaction between herbal and anti-cancer drugs, they should make an intervention immediately.

Table 2. Attitude of the cancer patients towards using herbal products/medicines

	Agree n (%)	Disagree n (%)	Neutral n (%)	Score (mean \pm SD)
1. Herbal medicines/products strengthen the immune system.	33 (60%)	21 (38.20%)	1 (1.80%)	2.22 \pm 0.98
2. Herbal medicines and products are more affordable than other treatments.	27 (49.10%)	22 (40%)	6 (10.90%)	2.09 \pm 0.95
3. Herbal medicines/products are safer than using other treatments.	17 (30.90%)	36 (65.50%)	2 (3.65%)	1.65 \pm 0.93
4. Herbal medicines/products are at least as effective as chemotherapy.	8 (14.50%)	40 (72.70%)	7 (12.70%)	1.42 \pm 0.74
5. Herbal medicines/products are better than chemotherapy.	2 (3.60%)	49 (89.10%)	4 (7.30%)	1.15 \pm 0.45
6. Herbal medicines/products reduce the side effects of chemotherapy.	22 (40%)	29 (52.70%)	4 (7.30%)	1.87 \pm 0.96
7. Herbal medicines/products are helpful in reducing the pain and fatigue caused by chemotherapy.	17 (30.90%)	33 (60%)	5 (9.10%)	1.71 \pm 0.92
8. Herbal medicines/products are helpful in reducing nausea and vomiting caused by chemotherapy	19 (34.50%)	32 (58.20%)	4 (7.30%)	1.76 \pm 0.94

SD: Standard deviation.

In a study conducted in Palestine in 2016, patients with breast cancer stated that they used herbal remedies to fight cancer at a high rate, as they believed they strengthened the immune system.¹⁴ In this study, 60% of cancer patients stated that herbal medicines/products strengthen the immune system, which supports the results of the previous study. On the other hand, 65.5% of cancer patients stated that the use of herbal products is not safe during chemotherapy. They may be concerned about possible interactions between anti-cancer agents and herbal products.

Samuels et al.¹⁵ showed that 41.3% of patients with breast cancer were using herbal medicine for cancer-related goals, unmonitored by their oncology healthcare professional. In this study, cancer patients were using herbal products/medicines without supervision from healthcare professionals. Cancer patients may not want to reveal that information because healthcare professionals prefer that patients not use herbal products.

Engdal et al.¹⁶, showed that 37% of palliative and 38% of curative patients used herbal remedies concurrent with chemotherapy. They also reported that one palliative patient detected adverse effects when doubling the dose of injected mistletoe used. Therefore, healthcare

professionals can detect herbal product use during pre- and post-chemotherapy by asking detailed questions about the amount, time, and frequency of use of herbal products/medicines by cancer patients. Thus, they may prevent the interaction of anticancer agents and herbal products/medicines.

The findings of this study showed that although cancer patients had low attitudes towards the use of herbal products, they still used them. This situation may indicate that cancer patients have used herbal products in addition to supportive drugs to reduce the side effects caused by chemotherapy or have done so due to drug shortages in purchasing supportive care drugs used to prevent side effects.

Study Limitations

This study had some limitations. First, the number of cancer patients included in this study was low, as it was conducted in a single centre. Therefore, we recommend that future studies should be multi-center. Cancer patients may have overestimated or underestimated their responses when responding to the attitude assessment questionnaire due to their health situation and potential bias.

Table 3. Association between demographic factors and cancer patients' attitude towards using medicines/products

	Good n	Poor n	Total n	%	p-value
Gender					
Male	5	14	19	34.50%	0.351
Female	14	22	36	65.50%	
Age					
<65 years	7	21	28	51%	0.130
≥65 years	12	15	27	49%	
Education status					
Primary school	5	7	12	21.80%	0.068
High school	4	19	23	41.80%	
University	10	10	20	36.40%	
Living place					
City	13	19	32	58.20%	0.263
Village	6	17	23	41.80%	
*p<0.05 was considered the statistically significant association between demographic factors and the cancer patients' attitude towards using herbal products as determined by the Pearson chi-square test.					

Table 4. Association between cancer patients' attitudes and herbal medicines/products users

Attitude level	Herbal medicines/ products users		p-value
	Yes n (%)	No n (%)	
Good attitude	11 (35.5%)	8 (33.3%)	0.868
Poor attitude	20 (64.5%)	16 (66.7%)	
Total	31 (100%)	24 (100%)	

*p<0.05 indicated a statistically significant association between users of herbal medicines and products and the cancer patients' attitudes towards using herbal products, as determined by the Pearson chi-square test.

Table 5. Herbal medicines/products used by cancer patients

Herbal medicines/products	Number of cancer patients using n	Percentage (%)
1. Cinnamon tea, <i>Cinnamomum cassia</i> Blume and <i>Cinnamomum verum</i> J. Presl	8	14.54%
2. Carob molasses, <i>Ceratonia siliqua</i>	6	10.9%
3. Ginger tea, <i>Zingiber officinale</i> Roscoe	5	9.1%
4. Turmeric powder, <i>Curcuma longa</i> L.	5	9.1%
5. Sage tea, <i>Salvia officinalis</i> L.	5	9.1%
6. Green tea, <i>Camellia sinensis</i>	4	7.3%
7. Fennel tea, <i>Foeniculum vulgare</i>	4	7.3%
8. Peppermint tea, <i>Mentha piperita</i> L.	3	5.45%
9. Linden tea, <i>Tilia Cordata</i>	2	3.63%
10. Chamomile tea, <i>Matricaria recutita</i> L.	2	3.63%
11. Passionflower tea, <i>Passiflora incarnata</i> L.	2	3.63%
12. Eucalyptus tree oil, <i>Eucalyptus globulus</i>	2	3.63%
13. Lemon balm/Melissa tea, <i>Melissa officinalis</i>	2	3.63%
14. Artichoke capsule, <i>Cynara scolymus</i> L.	2	3.63%
15. Echinacea tea, <i>Echinacea purpurea</i>	2	3.63%
16. Ginkgo capsule, <i>Ginkgo biloba</i> L.	2	3.63%
17. Blueberry/bilberry tea, <i>Vaccinium myrtillus</i> L.	1	1.8%
18. Aniseed tea, <i>Pimpinella anisum</i> L.	1	1.8%
19. Pomegranate seed oil, <i>Punica granatum</i>	1	1.8%
20. Nettle tea, <i>Urtica dioica</i> L.	1	1.8%
21. Black cumin seeds, <i>Nigella sativa</i>	1	1.8%
22. Flaxseed tea, <i>Linum usitatissimum</i> L.	1	1.8%
23. Cumin powder, <i>Cuminum cyminum</i>	1	1.8%
24. Black Elder tea, <i>Sambucus nigra</i> L.	1	1.8%
Cancer patients may use more than one herbal product/medicine.		

Table 6. Interaction between anti-cancer drugs and herbal medicines/products

Anti-cancer drugs	Herbal medicines/products	Medscape.com drug interaction checker	Drugs.com drug interaction checker
Bendamustine/rituximab	Green tea, <i>Camellia sinensis</i>	No interaction	No interaction
Docetaxel/cyclophosphamide	Ginger tea, <i>Zingiber officinale</i> Roscoe	No interaction	No interaction
Docetaxel/cyclophosphamide	Blueberry/bilberry tea, <i>Vaccinium myrtillus</i> L.	No interaction	No interaction
Irinotecan	Lemon balm/Melissa tea, <i>Melissa officinalis</i>	No interaction	Not available
Trastuzumab	Aniseed tea, <i>Pimpinella anisum</i> L.	Not available	Not available
Trastuzumab	Linden tea, <i>Tilia Cordata</i>	Not available	Not available
Trastuzumab	Chamomile tea, <i>Matricaria recutita</i> L.	Not available	No interaction
Docetaxel/cisplatin/fluorouracil	Green tea, <i>Camellia sinensis</i>	No interaction	No interaction
Docetaxel/cisplatin/fluorouracil	Fennel tea, <i>Foeniculum vulgare</i>	No interaction	No interaction
Docetaxel/cisplatin/fluorouracil	Peppermint tea, <i>Mentha piperita</i> L.	Not available	No interaction
Paclitaxel/carboplatin	Sage tea, <i>Salvia officinalis</i> L.	No interaction	Not available
Gemcitabine/cisplatin	Peppermint tea, <i>Mentha piperita</i> L.	Not available	No interaction
Paclitaxel	Cinnamon tea, <i>Cinnamomum cassia</i> Blume and <i>Cinnamomum verum</i> J. Presl.	No interaction	No interaction
Paclitaxel	Fennel tea, <i>Foeniculum vulgare</i>	No interaction	No interaction
Paclitaxel	Flaxseed tea, <i>Linum usitatissimum</i> L.	No interaction	Not available
Irinotecan/fluorouracil/leucovorin/bevacizumab	Peppermint tea, <i>Mentha piperita</i> L.	Not available	No interaction
Irinotecan/fluorouracil/leucovorin/bevacizumab	Artichoke capsule, <i>Cynara scolymus</i> L.	Not available	Not available
Pemetrexed/nivolumab	Green tea, <i>Camellia sinensis</i>	No interaction	No interaction
Paclitaxel/carboplatin	Turmeric powder, <i>Curcuma longa</i> L.	No interaction	No interaction
Gemcitabine/carboplatin	Turmeric powder, <i>Curcuma longa</i> L.	No interaction	No interaction
Gemcitabine/carboplatin	Passion flower tea, <i>Passiflora incarnata</i> L.	No interaction	Not available
Bortezomib	Sage tea, <i>Salvia officinalis</i> L.	No interaction	Not available
Bortezomib	Ginger tea, <i>Zingiber officinale</i> Roscoe	No interaction	No interaction
Bortezomib	Cinnamon tea, <i>Cinnamomum cassia</i> Blume and <i>Cinnamomum verum</i> J. Presl.	No interaction	No interaction
Bortezomib	Black elder tea, <i>Sambucus nigra</i> L.	No interaction	Not available
Bortezomib	Eucalyptus tree oil, <i>Eucalyptus globulus</i>	No interaction	Not available
Gemcitabine/bevacizumab	Turmeric powder, <i>Curcuma longa</i> L.	No interaction	No interaction
Gemcitabine/bevacizumab	Carob molasses, <i>Ceratonia siliqua</i>	Not available	Not available
Fluorouracil/leucovorin/oxaliplatin	Eucalyptus tree oil, <i>Eucalyptus globulus</i>	Monitor closely: <i>Eucalyptus</i> increases levels of fluorouracil	Not available
Fluorouracil/leucovorin/oxaliplatin	Sage tea, <i>Salvia officinalis</i> L.	No interaction	Not available
Fluorouracil/leucovorin/oxaliplatin	Turmeric powder, <i>Curcuma longa</i> L.	No interaction	No interaction
Fluorouracil/leucovorin	Carob molasses, <i>Ceratonia siliqua</i>	Not available	Not available
Paclitaxel/trastuzumab/pertuzumab	Ginger tea, <i>Zingiber officinale</i> Roscoe	No interaction	No interaction
Paclitaxel/trastuzumab/pertuzumab	Turmeric powder, <i>Curcuma longa</i> L.	No interaction	No interaction
Paclitaxel/trastuzumab/pertuzumab	Pomegranate seed oil, <i>Punica granatum</i>	Not available	Not available
Docetaxel	Chamomile tea, <i>Matricaria recutita</i> L.	Not available	No interaction
Docetaxel	Nettle tea, <i>Urtica dioica</i> L.	No interaction	No interaction
Trastuzumab/pertuzumab	Sage tea, <i>Salvia officinalis</i> L.	No interaction	Not available
Trastuzumab/pertuzumab	Ginger tea, <i>Zingiber officinale</i> Roscoe	No interaction	No interaction
Trastuzumab/pertuzumab	Turmeric powder, <i>Curcuma longa</i> L.	No interaction	No interaction
Trastuzumab/pertuzumab	Fennel tea, <i>Foeniculum vulgare</i>	No interaction	No interaction
Gemcitabine/cisplatin/bevacizumab	Passion flower tea, <i>Passiflora incarnata</i> L.	No interaction	Not available
Liposomal doxorubicin/bevacizumab	Turmeric powder, <i>Curcuma longa</i> L.	No interaction	No interaction
Liposomal doxorubicin/bevacizumab	Cinnamon tea, <i>Cinnamomum cassia</i> Blume and <i>Cinnamomum verum</i> J. Presl.	No interaction	No interaction

Anti-cancer drugs	Herbal medicines/products	Medscape.com drug interaction checker	Drugs.com drug interaction checker
Liposomal doxorubicin/bevacizumab	Green tea, <i>Camellia sinensis</i>	No interaction	No interaction
Docetaxel/cyclophosphamide	Ginger tea, <i>Zingiber officinale</i> Roscoe	No interaction	No interaction
Docetaxel/cyclophosphamide	Cinnamon tea, <i>Cinnamomum cassia</i> Blume and <i>Cinnamomum verum</i> J. Presl.	No interaction	No interaction
Docetaxel/cyclophosphamide	Turmeric powder, <i>Curcuma longa</i> L.	No interaction	No interaction
Docetaxel/cyclophosphamide	<i>Echinacea</i> tea, <i>Echinacea purpurea</i>	No interaction	Moderate interaction with docetaxel and cyclophosphamide medications: <i>Echinacea</i> may alter the blood levels and effects of docetaxel and cyclophosphamide
Ado-trastuzumab emtansine	<i>Echinacea</i> tea, <i>Echinacea purpurea</i>	No interaction	No interaction
Ado-trastuzumab emtansine	Cinnamon tea, <i>Cinnamomum cassia</i> Blume and <i>Cinnamomum verum</i> J. Presl.	No interaction	No interaction
Ado-trastuzumab emtansine	Fennel tea, <i>Foeniculum vulgare</i>	No interaction	No interaction
Ado-trastuzumab emtansine	Lemon balm/melissa tea, <i>Melissa officinalis</i>	No interaction	Not available
Ado-trastuzumab emtansine	Turmeric powder, <i>Curcuma longa</i> L.	No interaction	No interaction
Ado-trastuzumab emtansine	Ginger tea, <i>Zingiber officinale</i> Roscoe	No interaction	No interaction
Ado-trastuzumab emtansine	Black cumin seeds, <i>Nigella sativa</i>	Not available	Not available
Gemcitabine/cisplatin	Sage tea, <i>Salvia officinalis</i> L.	No interaction	Not available
Gemcitabine/cisplatin	Linden tea, <i>Tilia Cordata</i>	Not available	Not available
Fluorouracil/leucovorin/oxaliplatin	Cinnamon tea, <i>Cinnamomum cassia</i> Blume and <i>Cinnamomum verum</i> J. Presl.	No interaction	No interaction
Fluorouracil/leucovorin/oxaliplatin	Carob molasses, <i>Ceratonia siliqua</i>	Not available	Not available
Fluorouracil/leucovorin/oxaliplatin/docetaxel	Carob molasses, <i>Ceratonia siliqua</i>	Not available	Not available
Fluorouracil/leucovorin/oxaliplatin/docetaxel	Cumin powder, <i>Cuminum cyminum</i>	Not available	Not available
Doxorubicin/cyclophosphamide	Ginkgo capsule, <i>Ginkgo biloba</i> L.	No interaction	No interaction
Paclitaxel/trastuzumab	Ginkgo capsule, <i>Ginkgo biloba</i> L.	No interaction	No interaction

CONCLUSION

This study showed that cancer patients' attitudes toward herbal product use were poor. Cancer patients with poor attitudes were found to use more herbal products than cancer patients with good attitudes. Therefore, the interaction between herbal medicines/products and anti-cancer agents should be checked and thoroughly investigated by oncologists and oncology pharmacists using more than one drug interaction checker database.

MAIN POINTS

- Herbal medicines and products are used by cancer patients throughout their cancer treatment to mitigate the side effects of anti-cancer drugs.
- Healthcare professionals should explain to cancer patients the potential drug-herbal interactions that herbal products may cause in detail.
- Healthcare professionals should use more than one drug interaction checking program when checking for interactions between herbs and drugs.

ETHICS

Ethics Committee Approval: The Institutional Review Board of Near East University approved this study (approval number: 2022/102, date: 28.04.2022).

Informed Consent: All participants were informed about the aim of the study and provided verbal consent to the researchers before participating.

Footnotes

Authorship Contributions

Concept: N.B., A.S.B., Design: N.B., A.S.B., Data Collection and/or Processing: N.B., A.M., Analysis and/or Interpretation: N.B., A.S.B., Literature Search: N.B., A.S.B., A.M., Writing: N.B., A.S.B., A.M.

DISCLOSURES

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The Effect of Sexual Health Education on Men's Attitudes Towards Condom Use Among Youth Group in Jos, Nigeria

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Abstract

BACKGROUND/AIMS: Globally, unwanted pregnancies, unsafe abortions, and sexually transmitted infections continue to pose a significant public health challenge, with far-reaching personal and social consequences. To address these challenges, prioritizing a primary prevention strategy is crucial, the most widely supported strategy is condom use. This study aimed to determine the effect of health education on men's attitudes towards condom use in Jos, Nigeria.

MATERIALS AND METHODS: This is a quasi-experimental study utilizing 115 respondents as the sample. All the participants are members of the town fellowship youth group. In line with previous studies and the Multidimensional Condom Attitudes Scale, a sociodemographic questionnaire was used for data collection.

RESULTS: The majority were sexually active and had their first sex at the age of 18 years and below. In four out of the five attitude sub-scales (effectiveness, stigma, embarrassment about negotiation, and purchasing condoms), the results suggest a statistically significant difference between the pre-test and post-test scores for these sub-scales ($p < 0.01$). In comparing the pre and post-test scores for the pleasure associated with condom use, the results showed a non-statistically significant ($p < 0.06$) difference even with the mean post-test increase.

CONCLUSION: It is evident that providing sexual health education to the young sexually active men in this study has a positive effect and increases their attitude towards partner negotiation tactics and condom use. Further research is needed with a larger sample and a broader geographical area to help improve understanding of sexual health practices such as attitudes and pleasure associated with condom usage.

Keywords: Sexually transmitted infections, sexual health education, condom use attitude, young men

INTRODUCTION

Globally, unwanted pregnancies, unsafe abortions, and sexually transmitted infections (STIs) keep on posing a significant public health challenge, with far-reaching personal and social consequences.^{1,2} Each year, an estimated 374 million new cases of STIs are reported worldwide. The World Health Organization (WHO) reports that approximately one million new cases of STIs are acquired daily, and a considerable portion of these are asymptomatic.³ Several factors contribute to this persistent challenge, including insufficient condom use,⁴ inadequate

understanding of condom correct usage, fitting, and disposal methods, and, recently, the rise of drug resistance to conventional STI therapy.⁵

In Nigeria, where the human immunodeficiency virus (HIV) epidemic remains a critical concern, over 1.9 million individuals are currently living with HIV, with an adult prevalent rate of 1.4%;⁶ plateau state falls within the category of states with a medium prevalence rate (1.0 and 1.9%) which requires a targeted intervention to strengthen prevention and control measures.⁵ Among these measures, consistent and correct condom use is one of the best ways of reducing unwanted pregnancies,

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unsafe abortion, and the spread of STIs, including HIV.^{6,7} Male condoms are reported to be 98% effective in preventing STIs, teenage pregnancies, and unwanted pregnancies;⁸ however, their effectiveness is often reduced by errors during use and inconsistent application.^{9,10}

Despite the common awareness of the benefits of condoms among youth,¹¹ studies reveal that the use of condoms remains inconsistent, especially among the Nigerian youth.¹²⁻¹⁴ Identified barriers to consistent condom use include misconceptions, cultural stigmas, affordability, availability, latex allergies and perceptions of reduced sexual pleasure about condom use; furthermore, reliance on partners' decisions and societal mistrust of condoms increased these issues^{13,14} thereby exposing youth to a higher risk of impaired sexual and reproductive health outcomes such as unwanted pregnancies, teenage pregnancies, unsafe abortions and STIs including HIV/acquired immunodeficiency syndrome (AIDS).¹⁵

Psychosocial factors, especially attitude, are significant in determining condom use behaviors.^{16,17} Existing findings suggest that an individual's attitude toward using condoms significantly determines their actual use.¹⁸ Positive attitudes towards condoms are strongly linked with healthier sexual behaviors, including consistent and correct condom use; in contrast, a negative attitude often leads to reduced condom use,^{16,19,20} and engagement in harmful sexual practices such as unprotected intercourse with more than one partner.¹⁴ Importantly, studies reported sexual health education that did not address attitude often showed limited success in improving consistent and correct condom use.²¹

While alternative sources of sexual health information such as digital media and peer education are available to youth, these methods face challenges related to information accuracy, cultural influences, and individual education levels.^{22,23} Comprehensive sexuality education offers a more holistic and rights-based approach to addressing sexual and reproductive health issues. However, its implementation in Nigeria faces challenges such as cultural and/religious resistance, inadequate training, and policy gaps. Therefore, sexual health education delivered by health professionals using interactive lectures, group discussions, role play, and condom use demonstrations in the form of targeted interventions has a higher chance of providing education to address specific misconceptions and barriers. This, in addition to other benefits such as confidentiality and professionalism, suggests that this study utilized this approach.

Existing literature in Nigeria largely consists of non-interventional studies focusing on knowledge, barriers, and predictors of condom use.¹¹⁻¹⁵ Literature searches did not reveal any interventional study that explored the effectiveness of sexual health education in improving attitudes toward condom use. Although international studies have explored the impact of sexual health education on reducing sexual risks^{24,25} and self-efficacy for correct condom use,²⁶ there remains a research gap in addressing attitude-based interventions among young men in the Nigerian context.

Research Aim and Hypotheses

This study aims to determine the effect of sexual health education on men's attitudes toward condom use in Jos, Nigeria. The following hypotheses guided the study.

H0: There is no significant difference in participants' Multidimensional Condom Attitude Scale (MCAS) sub-scale scores for the reliability and effectiveness of condoms before and after the intervention.

H0: There is no significant difference in participants' MCAS sub-scale scores for pleasure associated with condoms before and after the intervention.

H0: There is no significant difference in participants' MCAS sub-scale scores for stigma associated with condoms before and after the intervention.

H0: There is no significant difference in participants' MCAS sub-scale scores for embarrassment about negotiation and use of condoms before and after the intervention.

H0: There is no significant difference in participants' MCAS sub-scale scores for embarrassment about purchasing condoms before and after the intervention.

MATERIALS AND METHODS

Study Design

The research used a quasi-experimental study design with a pre-test and post-test paired group pattern.

Study Place and Characteristic

The study was carried out at the Odus community in Jos, Nigeria, between September 2021 and December 2021. Odus is a community with a large youth population due to its closeness to the University of Jos. In addition, the participants are members of the town fellowship youth group, which brings together youth from different sections of the Odus community to discuss issues beneficial to the youth and the community.

Sample Size and Sampling Technique

The sample size was calculated using the Taro Yamane sample size formula. With a total youth population of 152, a 5% margin of error resulted in a sample of 110 participants. To ensure sufficient participant numbers and account for attrition, the sample size was increased by 10%, resulting in 121 participants. This decision was informed by a previous study with the same sample size,²⁵ which demonstrated a medium effect size. Participants were selected using convenience sampling, adhering to predefined inclusion and exclusion criteria.

Inclusion Criteria: Being 18 years old or above, male, and accepting to join the survey.

Exclusion Criteria: Had sexual health education or training for HIV/AIDS peer educator, unable to speak English, and not a town fellowship youth group member. Three participants voluntarily withdrew from the study, and three did not complete the training and the post-test; therefore, the final sample for the study was 115 participants.

Study Instruments

A sociodemographic and sexual profile questionnaire in line with previous related studies,^{11,14} was used to obtain sociodemographic information (5 items) and sexual profiles of the participants (9 items).

Multidimensional Condom Attitude Scale

Helweg-Larsen and Collins²⁷ developed the MCAS English version that measures condom attitudes in 5 different sub-scales, each with five items for a total of 25 items. The five sub-scales and the items are: (1) reliability and effectiveness of condoms (items 4, 6, 9, 14, and 20); (2) pleasure associated with condoms (items 2, 8, 15, 19, and 25); (3) stigma associated with condoms (items 3, 13, 18, 22, and 24); (4) embarrassment about negotiation and use of condoms (items 1, 7, 12, 16, and 21) and lastly, (5) embarrassment about purchasing condoms (5, 10, 11, 17, and 23). Reliability of the scale was established, indicating internal consistency in 3 different studies using both factor and confirmatory factor analysis in structural equation modeling, demonstrating adequate Cronbach's alpha values ranging from. Seventy-one to 94 for each factor. Construct and criterion validity for the MCAS was established as well.^{28,29} Some MCAS items are worded negatively, and the score must be reversed before adding and averaging the scores; the items were measured using a 7-7-point scale ranging from (1-strongly disagree) to (7-strongly disagree). After reversing the score for negatively worded items, the minimum score for each sub-scale is seven, and the maximum is thirty-five, and higher scores indicate more positive condom attitudes. Each sub-scale is scored separately; the sub-scale score is calculated as the sum of the five items divided by 5. The sub-scale score ranges from 1 (most negative attitude) to 7 (most positive attitude).

Research Process

Figure 1 shows the application phase of the research process, providing a comprehensive flowchart. The study's data collection and implementation process spanned six weeks: details of each week's activities are shown in the figure.

Research Intervention

The sexual health education was planned in 5 sessions, and intervention content was based on published research reviews and resources from

WHO, CDC and UNESCO^{3,22,23,30}, also, expert opinions from 2 public health nurses, 2 gynaecology and obstetrics nurses, and 1 internal medicine nurse were sought. The sessions were conducted using lectures, edutainment, brainstorming, an interactive group discussion format, PowerPoint, video/infographics presentations, demonstrations/hands-on activities, and role-play, designed to encourage participation and emphasize the educational content. The sexual health education consists of five pieces of content delivered once a week for week 3 and twice for weeks 4 and 5. The intervention for each piece of content took a period of 2 hours and was delivered by the second author. The details of the content of each session of the intervention are shown in the dossier, which is attached as supplementary material.

Ethical Considerations

Ethical approval for this study has been obtained from the Near East University Ethics Committee (approval number: 2020/79, date: 08.05.2020) and the town fellowship youth group management, as well as for the use of the MCAS. Informed consent was obtained from all participants, ensuring their confidentiality, voluntary participation, and right to withdraw at any point in the study.

Statistical Analysis

The Statistical Package for Social Sciences version 22.0 statistical program was used to evaluate the data. Data normality was assessed using the Kolmogorov-Smirnov test, revealing a non-normal distribution. The socio-demographic characteristics of the respondents were described using frequency and percentages. The Wilcoxon signed-rank test was used to analyze the intervention's effect on youth condom attitudes, with significance determined at $p < 0.05$.

RESULTS

Table 1 shows that 67.82% ($n=78$) of the participants were between 21-30 years old, 58.26% ($n=67$) were Nigerian, 69.56% ($n=80$) were single,

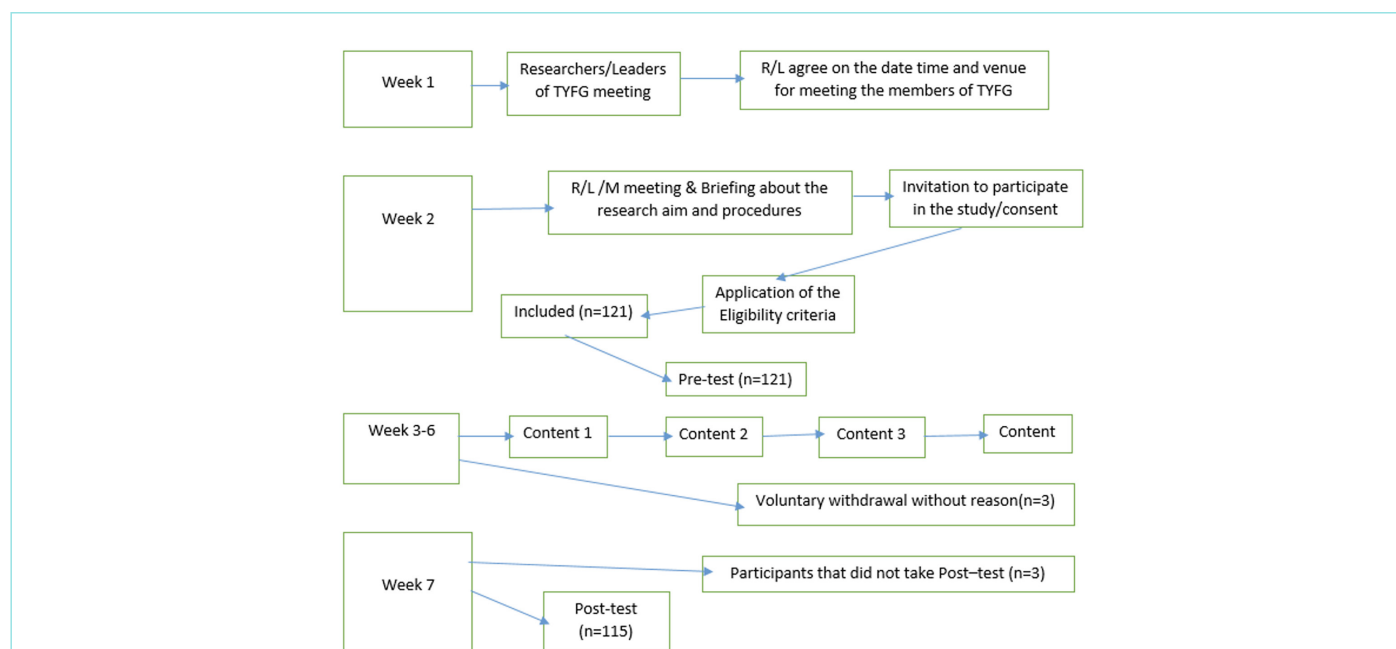


Figure 1. The Flowchart of the application phase of the research.

94.78% (n=109) had university education, and 44.34% (n=51) had middle-income level.

Based on the results in Table 2, 92.17% (n=106) of the participants had engaged in sexual intercourse previously, 60.0% (n=69) were sexually active in the last three months, 30.43% (n=35) had three or more partners in the previous three months, 71.30% (n=82) used condoms during intercourse, 44.34% (n=51) received condom information from school, 59.13% (n=68) used condoms to protect themselves from sexually transmitted diseases, 62.21% (n=75) usually had vaginal sex with condoms, and 60.86% (n=70) bought condoms from pharmacies.

The results provided in Table 3 above show the pre-test and post-test average and standard deviation scores of the participants from the MCAS sub-dimensions, the reliability and effectiveness of condoms sub-dimension had a pre-test (21 ± 0.23), and post-test (25.5 ± 0.20) score; the pleasure associated with condoms sub-dimension had a pre-test score of (18 ± 0.18) and a post-test score of (23.5 ± 0.18). The stigma associated with condom use sub-dimension had a pre-test (21 ± 0.25) and post-test (25 ± 0.28) score. On the aspect of embarrassment about negotiation and the use of the condom sub-dimension scale, the respondents had a pre-test (20 ± 0.24) and post-test (23 ± 0.21) score. Lastly, the respondents had pre-test (11 ± 0.15) and post-test (16.5 ± 0.13) scores on the Embarrassment about Purchasing Condoms Sub-dimension Scale. Across all sub-scales, the post-test scores are consistently higher than the pre-test scores. The lowest score was observed in embarrassment about purchasing condoms, which still indicates a negative attitude. The standard deviations across all sub-scales remain small, suggesting consistency in participants' responses in each sub-scale.

Table 4 above presents a comparison of median scores on different sub-scales related to condom attitudes and behaviours of the respondents before and after sexual health education. The p-value indicates the level of significance of the difference observed. In four out of the five attitude sub-scales (reliability and effectiveness, stigma associated with condom use, embarrassment about negotiation and use of condoms, and embarrassment about purchasing condoms), the results suggest a statistically significant difference between the pre-test and post-test scores for these sub-scales ($p < 0.01$). Hence, the null hypotheses were rejected for the aforementioned sub-scales. This shows the intervention had a notable impact on these aspects of participants' attitudes towards

condom use. However, when comparing the pre and post-test scores for the pleasure associated with condom use sub-scale of MCAS, the results indicate the difference is not statistically significant ($p < 0.06$) even though the median post-test score is greater than the median of the pre-test score, hence, the null hypothesis is not rejected for this sub-scale.

DISCUSSION

The study was carried out to examine the effect of sexual health education on men's attitudes towards condom use. Regarding sexual activity, the majority were sexually active. Among the sexually active cohorts, most engaged in sexual activity for the first time at the age of 18 years and below. The above results are consistent with previous studies on condom use.^{9,15}

The findings of the study showed a comparison of mean scores on different sub-scales related to condom attitudes and behaviours of the respondents before and after an intervention program. Participants demonstrated mixed attitudes: positive attitudes were observed regarding the reliability and effectiveness of condoms, the stigma associated with condom use, and embarrassment about negotiation and

Table 2. Sexual profile of participants (n=115)

Variables		n	%
Had sexual intercourse	Yes	106	92.17
	No	9	7.82
Sexual activities	Active in past 3 months	69	60.00
	Not active in past 3 months	46	40.00
Number of partners in last three months	0	42	36.52
	1	24	20.86
	2	14	12.17
	3+	35	30.43
Condom usage during intercourse	Yes	83	72.13
	No	32	27.82
Knowledge of condom usage	School	51	44.34
	Home	29	25.21
	Hospital	35	30.43
Reason of condom use	STDs prevention	68	59.13
	Pregnancy prevention	41	35.65
	Others	6	5.21
STDs History	Never	90	78.26
	Once	9	7.82
	Twice	16	13.91
General sex intercourse	Vaginal with condom	75	65.21
	Vaginal without condom	24	20.86
	Oral with condom	7	6.08
	Anal with condom	9	7.82
Site of purchase	Market	18	15.65
	Pharmacy	70	60.86
	Internet	21	18.26
	Others	6	5.21

STDs: Sexually transmitted diseases.

Table 1. Socio-demographics characteristics of participants (n=115)

Variables		n	%
Age	18-20	30	26.08
	21-30	78	67.82
	31+	7	6.08
Race	Afro-American	23	20.00
	Nigerian	67	58.26
	Others	25	21.73
Marital status	Single	80	69.56
	Married	35	30.43
Education	University education	109	94.78
	Graduate studies	6	5.21
Economic status	Low	40	34.78
	Middle	51	44.34
	High	24	20.86

Table 3. Pre and post-test means of participants from MCAS sub-scales

Sub-scale			Pre-test			Post-test		
	Min.	Max.	Min.	Max.	Mean \pm SD	Min.	Max.	Mean \pm SD
Reliability and effectiveness of condoms	5	35	17	25	21.0 \pm 0.23	20	31	25.5 \pm 0.20
Pleasure associated with condoms	5	35	16	20	18.0 \pm 0.18	18	29	23.5 \pm 0.18
Stigma associated with condom use	5	35	15	27	21.0 \pm 0.25	18	32	25.0 \pm 0.28
Embarrassment about negotiation and use of condom	5	35	13	27	20.0 \pm 0.24	16	30	23.0 \pm 0.21
Embarrassment about purchasing condoms	5	35	7	15	11.0 \pm 0.15	13	20	16.5 \pm 0.13

MCAS: Multidimensional Condom Attitude Scale, SD: Standard deviation, Min.: Minimum, Max.: Maximum.

Table 4. Pre and post-test comparison of participants scores from MCAS sub-scales

Sub-scale	Pre-test			Post-test				
	Min.	Max.	Mean \pm SD	Min.	Max.	Mean \pm SD	Z	p-value
Reliability and effectiveness of condoms	17	25	21.0 \pm 0.23	20	31	25.5 \pm 0.20	-8.59	p=0.01
Pleasure associated with condoms	16	20	18.0 \pm 0.18	18	29	23.5 \pm 0.18	1.88	p=0.06
Stigma associated with condom use	15	27	21.0 \pm 0.25	18	32	25.0 \pm 0.28	-8.06	p=0.01
Embarrassment about negotiation and use of condom	13	27	20.0 \pm 0.24	16	30	23.0 \pm 0.21	-8.43	p=0.01
Embarrassment about purchasing condoms	7	15	11.0 \pm 0.15	13	20	16.5 \pm 0.13	-8.36	p=0.01

MCAS: Multidimensional Condom Attitude Scale, SD: Standard deviation, Min.: Minimum, Max.: Maximum.

use of condoms, while negative attitudes were observed in: pleasure associated with condom use, and embarrassment about purchasing condoms. The baseline attitude scores were lower compared to studies.^{27,31,32} Notably, the “embarrassment about purchasing condoms” sub-scale had the lowest score, indicating the most negative attitude among the participants; this agrees with Cho’s results but contrasts with Stevlana’s results, where positive attitudes were reported across all the MCAS sub-scales.

The intervention program designed using diverse teaching methodologies and resources was effective in improving attitudes across most MCAS sub-scales. Significant positive changes in perceived reliability and effectiveness of condoms were noted post-intervention, suggesting participants gained accurate information through group discussions and educational media used. This aligns with findings of^{32,33}, which reported a significant increase in the same MCAS sub-scale post-intervention. The intervention significantly reduced the stigma associated with condom use, reflecting changing perceptions of an open sexual culture among the youths in the study; this outcome is consistent with Dubova’s study but differs from Cho’s, where the stigma score remained static after the intervention. Strategies such as interactive group discussions utilized during the intervention sessions empowered the participants to learn the skills of negotiating condom use effectively, consequently increasing the participant’s positive attitude toward negotiation for condom use; this is supported by Aggleton and Warwick’s³⁴ assertion that active participation of subjects is critical in sexual health education, related studies³⁵ also showed increased negotiation frequency after

the intervention. Additionally, this finding is in line with a previous finding that shows practicing condom negotiation strategies result in increasing the likelihood of using condoms and behavioral intentions^{25,36}, while findings of Reils²⁶ show condom education intervention enhances young and late adolescents’ sexual partner communications.

Limited improvements were observed in pleasure associated with condoms; while the attitude shifts slightly from negative to positive, the change was not significant; this finding agrees with^{11,37} studies, where participants reported that condoms reduced sexual pleasure, which may be attributed to the age and preferences of the study participants, the finding also further aligns with previous research findings, that many youth provides loss of pleasure as justifications for not using condoms and the anticipation of partner rejection.³⁸ Regarding embarrassment about purchasing condoms, although there was a significant improvement in the participant’s score, the attitude still remained negative. Researchers result in two separate studies^{39,40} opined that embarrassment tendencies are affected by societal stigma; participants continued to feel uneasy about purchasing condoms despite gaining knowledge of youth-friendly services; further studies may address this issue by promoting more discrete access points and reducing societal prejudice.

Study Limitations

Considering the limitation of the study to a single site geographic location, the findings of the study may not be generalizable to the entire Jos Plateau and especially in settings with different cultural norms,

beliefs, and attitudes regarding condoms; however, this environment did offer a unique chance to connect with an underserved group of young, heterosexual, sexually active young adults with multiple sex partners as seen from the sexual profile of the respondents in the study. Notwithstanding these limitations, the originality of this study reflects the influence of the sexual health education undertaken by a young medical professional. Through the intervention, young men were able to learn how to use condoms and negotiate condom use; this culturally sensitive intervention addressed the main concerns of the population of young heterosexual men who are sexually active. It improved conversations and comfort levels surrounding condoms and made it possible to develop and disseminate condom promotion techniques throughout society.

Implications and Future Directions

The study indicates the effect of sexual health education on improving young men's attitudes toward condom use, mainly regarding reliability, stigma reduction, and negotiation. However, minimal changes in perceptions of pleasure and persistent embarrassment about condom purchase indicate the need for targeted interventions. Future interventions should emphasize peer education, community engagement, anonymous or youth-friendly condom access, and evidence-based messaging to address misconceptions. The findings demonstrate the significance of sexual health education in promoting healthier sexual behaviors and contributing to the limited evidence on peer-led approaches. Further research with larger samples and broader geographical coverage is recommended to deepen understanding and encourage widespread adoption of accurate sexual health practices.

CONCLUSION

The results of the study reveal significant improvements in several key areas, suggesting that the intervention addressed common barriers associated with respondents' attitudes on reliability and effectiveness, lessened the stigma attached to using condoms, and reduced the embarrassment of negotiating and using condoms, thereby contributing to more positive attitudes and behaviors regarding condom use. However, the analysis also indicates that the intervention did not significantly impact the attitude toward pleasure associated with condom use, even though the median post-test scores were higher than the mean pre-test scores. Regarding embarrassment about purchasing condoms, although there was a significant improvement in the participant's score after the intervention, the attitude remained negative. Therefore, future interventions could benefit from incorporating strategies to emphasize the positive aspects of sexual experiences involving condoms, thereby promoting more comprehensive and positive attitudes toward condom purchase and use among participants.

MAIN POINTS

- The study found a significant change in participants' attitudes towards the reliability and effectiveness of condoms post-intervention, indicating the success of the intervention.
- Participants' perceptions of the pleasure associated with condom use changed from negative to positive after the intervention, though the change was not statistically significant.
- One of the most encouraging findings was a significant positive shift in participants' attitudes toward the stigma associated with condom

use, signifying a potential for societal change and reduced condom barriers.

- Attitudes toward negotiating and using condoms among the participants increased after the intervention, implying that the youth gained condom negotiation skills.
- Although the participants' attitudes regarding purchasing condoms increased after the intervention, they remained negative, indicating a barrier that needs further intervention.

ETHICS

Ethics Committee Approval: Ethical approval for this study has been obtained from the Near East University Ethics Committee (approval number: 2020/79, date: 08.05.2020).

Informed Consent: Informed consent was obtained from all participants, ensuring their confidentiality, voluntary participation, and right to withdraw at any point in the study.

Footnotes

Authorship Contributions

Concept: S.E., A.I., L.L.L., Design: S.E., A.I., Data Collection and/or Processing: A.I., L.L.L., Analysis and/or Interpretation: S.E., A.I., L.L.L., Literature Search: S.E., A.I., L.L.L., Writing: S.E., A.I., L.L.L.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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Bibliometric Analysis of Spiritual Healing Themed Articles in Nursing Research Area

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Abstract

BACKGROUND/AIMS: This bibliometric analysis aims to highlight important trends, research questions and contributions to better understand the academic literature on spiritual healing. Recognized as an important part of holistic nursing care, spiritual healing includes methods of treating spiritual dimensions of health and well-being and is now generally recognized.

MATERIALS AND METHODS: A systematic literature search was conducted to identify articles focussing on spiritual healing in the field of nursing. This search covered publications up to April 2024, and the Web of Science Core Collection database was used. A dataset of 878 articles was obtained as a result of the keyword search. Bibliometric analyses were performed with VosViewer software. Parameters such as number of publications, most productive countries/institutions, most cited articles, and top themes were analysed.

RESULTS: This study revealed that spiritual topics have increased significantly in the nursing literature since 2016. The geographical distribution analysis showed that the United States of America (USA) led the way in this field, with countries such as Iran, the United Kingdom and Brazil also making significant contributions. Loma Linda University and the University of São Paulo stood out among the institutions with the most publications. Keyword analysis highlighted the importance of topics such as “spirituality”, “nursing”, “patients”, and “palliative care”. Findings revealed a growing acceptance of spiritual healing in nursing practice, global collaboration, and research diversity.

CONCLUSION: The study highlights a global increase in nursing research on spiritual healing since 2016, with the USA leading the way.

Keywords: Spiritual healing, spirituality, nursing, publication

INTRODUCTION

Human beings are rich in biological, psychological, social and spiritual aspects. While each dimension is important for the well-being and health of the person, it is emphasized that the spiritual dimension, distinct from the physical, emotional, and social domains, plays a significant role. Spirituality is thought to have healing or therapeutic effects

in cases of illness.^{1,2} While there is currently no precise definition of spirituality, it is generally characterized as the process of understanding the meaning of life, setting goals and finding inner peace. Spirituality is also referred to as an integrative force that affects body, and soul.^{3,4} Spirituality constitutes a fundamental dimension of human existence and involves the process of relating oneself to an infinite being. This process manifests it self as a satisfying experience in the depths of life,

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a search for meaning and an effort to discover the purpose of life.⁴ In times of crisis or illness, the spiritual needs of individuals become more apparent. During these periods, people seek inner balance, support, and tend to turn to spiritual resources.⁵ In challenging times, such as crises or illness, individuals often turn to spiritual resources to cope.^{6,7} Prayer and religious practices are among the most common ways to achieve spiritual healing and peace.⁵ Spiritual healing is considered to be the oldest and most universally accepted method of complementary and alternative medicine, and is practiced in every culture worldwide.⁸ Although exactly how spiritual healing works has not yet been fully explained, it is an approach in which healing energy is used to benefit the individual's mind, body, and spirit.⁹ People can benefit from spiritual healing and other complementary and alternative medicine practices to get rid of diseases or maintain health.^{5,10} Research in recent years, shows that studies on spiritual healing and/or healing through prayer have increased and positive results have been obtained in this field. These studies examine the effects of people's spiritual beliefs and prayers on physical and mental health and emphasize the healing potential of such practices.^{5,10-12} Currently, nursing care also supports the philosophy of holistic care. Spiritual care is an integral part of this approach, which includes mental, physical, and spiritual dimensions. This approach encompasses the treatment process by considering not only the physical needs of patients but also their emotional and spiritual needs.¹³ Nurses need to be prepared and competent to protect, maintain, and improve the integrity of all dimensions of the individual's being. In this context, it is important that they are trained and equipped to meet the physical, emotional, mental, and spiritual needs of individuals. In particular, being aware of the spiritual needs of individuals and having knowledge about the nature of spirituality enables nurses to provide more effective spiritual care and provide holistic care. Therefore, the spiritual dimension has critical importance in nursing care, and adopting a conscious approach in this area contributes to the full recovery process of patients.^{1,14} Spiritual healing, as a critical part of holistic nursing care, is now generally recognized as encompassing methods to treat spiritual health and well-being.¹³

Nursing care and approach within the health system are becoming increasingly important. As with many subjects related to nursing care, it is guiding in terms of the efficiency of scientific studies to reveal existing publications on spiritual health and nursing care from various perspectives is beneficial for understanding the efficiency of scientific studies. This will only be possible by strengthening and enriching the literature. This research aims to evaluate the research productivity on spiritual health and nursing care approaches and to measure the impact of scientific quality. It intends to reveal previously published scientific studies, learn the number and quality of these studies that have the quality of evidence, and determine which types of studies are needed on this subject. Furthermore, it seeks to understand the status of scientific approaches to spiritual nursing care within the framework of different cultures and belief systems, identify trends in the field of research, monitor information dissemination and interaction, understand the collaboration networks of studies, and research needs, scientific insufficiencies and information deficiencies in the literature in the literature.^{8-10,14}

This bibliometric analysis explores trends, research questions, and contributions to spiritual healing in nursing. This study aimed to provide information about the current status and characteristics of the literature on spirituality in the field of nursing.

MATERIALS AND METHODS

Literature Search

Until April 1, 2024, a search of the Web of Science Core Collection search engine using the keywords MESH found 22,003 publications with titles such as "spiritual" OR "therapies, spiritual" OR "exorcism" OR "exorcisms" OR "spiritual healing" OR "healing, spiritual" OR "spiritual cures". Of these, 12,556 were identified as articles. Then, 878 articles focusing on the field of nursing were extracted to form the sample of the study. These 878 articles were identified as the data set for all analyses.

The aim of the search technique was to find important material related to spiritual issues in various fields such as exorcism, therapy, and healing methods. Publications in the field of nursing were examined to investigate the link between spirituality and health care, especially in terms of nursing practice. This group of articles provides the basis for further research and analysis on topics such as the role of spirituality in nursing care, its impact on patient outcomes, and its integration into healthcare delivery systems.

Ethical consideration: Ethical approval is not required as this study does not involve human or animal subjects. This publication was made using a free database. It also did not require informed consent as it was a literature review without human and animal samples.

Statistical Analysis

VOSviewer, developed by Van Eck and Waltman¹⁶, is a scientific mapping software that is widely discussed in publications regarding its functioning, data, and bibliometric methods. A VOSviewer manual is available to help users better understand the software. VOSviewer includes bibliometric terms that may not be familiar to some users. Co-authorship refers to collaborative publications among researchers, research centers, or countries. Density visualization maps show the size and impact of an area and are of two types: item and cluster. Item density maps show the density of items at a given point, while cluster density maps examine the density of a cluster.^{15,16}

The network visualization map shows clusters using a specific color, and each keyword is represented by a node in a color corresponding to its cluster. VOSviewer uses a statistical technique called probabilistic latent semantic analysis to identify important keywords. After this analysis, the relationships are examined in more detail through cluster analysis. Keywords are clustered due to their close relationship with each other, and keywords that appear in similar research are positioned closer to each other. VOSviewer also strives to prevent nodes from overlapping each other and highlights connections when a node is selected, which reduces the visibility of other nodes to show the network more clearly. Frequent use of a node increases the size of the node and the number of connections to other nodes.^{16,17}

Bibliometrics is a comprehensive quantitative analysis tool used to evaluate research based on research objectives. In this study, a systematic literature search was conducted to identify articles focusing on spiritual healing in the field of nursing. VOSviewer, developed by Van Eck and Waltman¹⁶, is a widely published scientific mapping software on its functioning, data and bibliometric methods. The VOSviewer 1.6.20 software was used to analyze and visualize the data. This approach aims to identify the current status of the field, research trends, and the most influential publications and researchers.¹⁸⁻²⁰

RESULTS

Publication Trends

The analysis of spiritual-themed articles in the nursing research field revealed a wide diversity spanning various historical periods. There had been a significant increase in nursing research on spiritual topics, with the highest percentages found to be 7.403%, 7.062%, and 7.403% in 2023, 2022, and 2021, respectively. The number of publications started to increase in 2016 and peaked in 2023. With the exception of a few publications dating back to 1978, there were far fewer publications before 1978. From 1978 to 2005, the number of spiritual themes in nursing research gradually increased, but the number of publications remained at low levels. From 2006 to 2015, there was a low-level increase, indicating that spiritual aspects in nursing care were receiving increasing attention. However, from 2016 onwards, there was a marked increase in the number of publications, with an upward trend in each year after 2016 (Figure 1).

According to the Web of Science database, articles on spirituality in the field of nursing research showed various distributions in different indexes. The majority of articles in this field were published in journals indexed in the Social Sciences Citation Index (68.679%) and journals indexed by the Science Citation Index Expanded (62.756%).

Citing Analysis

The study of spirituality in nursing research, found that religion was the most common citation topic, accounting for 75.171% of the total. Palliative care was the most significant topic, with 61 articles (6.948% of the total sample) indicating the connection between spiritual healing and end-of-life care. Nursing itself was a significant citation topic, with 25 articles (2.847%) highlighting its role in spiritual care. Other meso-level themes included psychiatry (1.822%), management (1.367%), obstetrics and gynecology (1.025%), and social psychology (0.911%). Niche areas like human immunodeficiency virus, substance abuse, cancer care, and complementary medicine were also included. This

highlights the multifaceted nature of spiritual healing in nursing and its relevance across various healthcare contexts (Table 1).

The study analyzed citation topics at the micro-level, revealing spirituality as the most prominent, accounting for 74.829% of the total. Other notable topics included palliative care, cancer survivors, and nursing. Mindfulness, job satisfaction, dementia caregivers, and breech presentation were also significant. Niche areas like peritoneal dialysis, post-traumatic stress disorder, autobiographical memory, and shared decision-making were also present. These findings highlight the multifaceted nature of spiritual healing research within nursing, encompassing various healthcare and human experiences (Table 2).

Top Cited Articles

Between 1970 and 2024, these works received a total of 15063 citations. The average number of citations for each item was 17.16, which shows how influential and relevant it was in its respective field. The current h-index is 56. There were 60 publications and 2582 citations in 2023. There were 65 publications and 2591 citations in 2021. As shown in Figure 1, most citations occurred in these particular years in Figure 1. Table 3 lists the top cited articles in spiritual healing-related literature in the nursing field. The top cited articles include “an online survey of nurses’ perceptions of spirituality and spiritual care” by McSherry and Jamieson²¹ from the *Journal of Clinical Nursing*, “spiritual care in nursing: an overview of the research to date” by Linda Ross²², “the crescent and Islam: healing, nursing and the spiritual dimension” by Rassool²³, “spiritual care in nursing: a concept analysis” by Ramezani et al.²⁴ from the *International Nursing Review*, and “The construct validity of a rating scale designed to assess spirituality and spiritual care” by McSherry et al.²⁵ from the *International Journal of Nursing Studies*.

Geographical Distribution, Co-Authorship Analysis Among Countries

A total of 60 countries had contributed to the literature on spiritual healing in nursing.

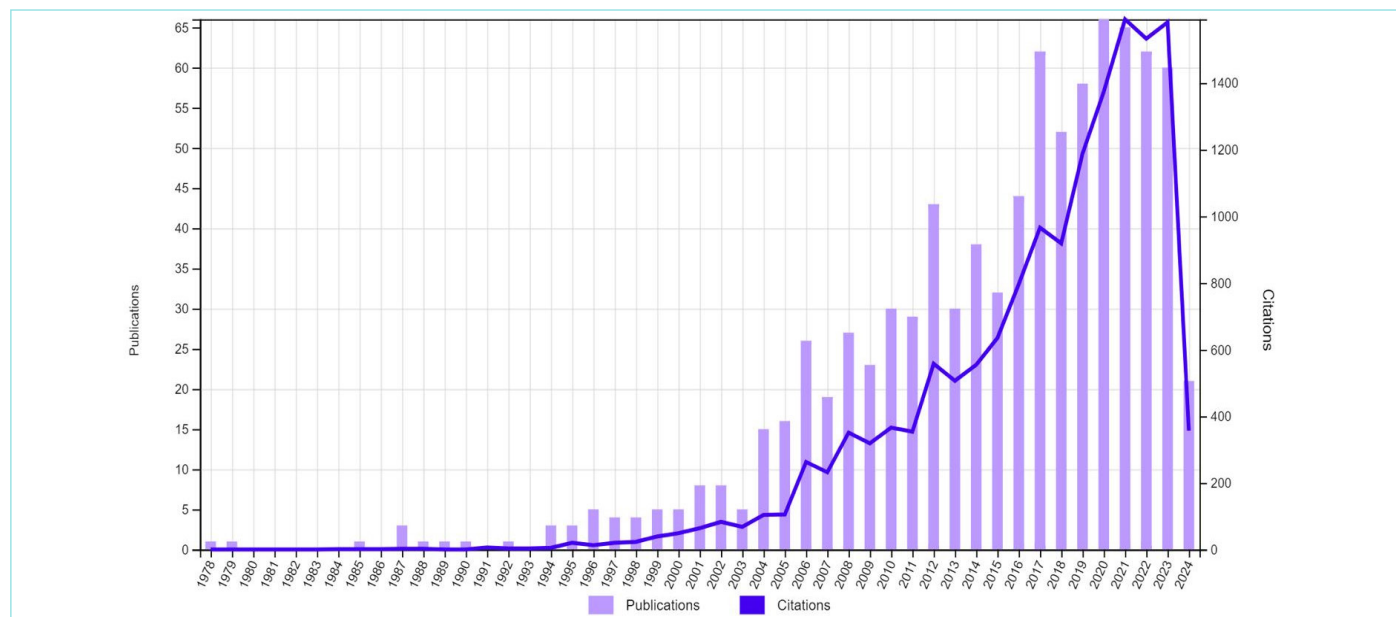


Figure 1. Time cited and publications over time.

Table 1. Citation topics meso

Citation topics meso	n	% of 878
Religion	660	75.171
Palliative care	61	6.948
Nursing	25	2.847
Psychiatry	16	1.822
Management	12	1.367
Obstetrics and gynaecology	9	1.025
Social psychology	8	0.911
Psychiatry and psychology	7	0.797
Healthcare policy	6	0.683
Urology and nephrology-general	5	0.569
HIV	3	0.342
Substance abuse	2	0.228
Liver and colon cancer	2	0.228
Breast cancer scanning	2	0.228
Assisted ventilation	2	0.228
Tuberculosis and leprosy	2	0.228
Autonomic regulation	2	0.228
Diabetes	2	0.228
Complementary and alternative medicine	2	0.228
Cardiology-general	2	0.228
Reproductive biology	2	0.228
Homelessness and human trafficking	2	0.228
Virology-general	1	0.114
Strokes	1	0.114
Rheumatology	1	0.114
Fertility, endometriosis and hysterectomy	1	0.114
Back pain	1	0.114
Trauma and emergency surgery	1	0.114
Autism and development disorders	1	0.114
Hormone therapy	1	0.114
Urology	1	0.114
Medical ethics	1	0.114
Vascular, cardiac and thoracic surgery	1	0.114
Hematologic diseases	1	0.114
Smoking cessation	1	0.114
Nerve disorders	1	0.114
Anaesthesiology	1	0.114
Nutrition and dietetics	1	0.114
Allergy	1	0.114
Bone diseases	1	0.114
Gait and posture	1	0.114
Philosophy	1	0.114
Music	1	0.114
Gender and sexuality studies	1	0.114
Operations research and management science	1	0.114
Statistical methods	1	0.114

*20 record(s) (2.278%) do not contain data in the field being analysed **Web of Science table. HIV: Human immunodeficiency virus.

The top 10 countries in terms of document contributions were the United States of America (USA) (331 documents, 37.70%), Iran (70 documents, 7.98%), England (68 documents, 7.74%), Brazil (61 documents, 6.95%), Canada (47 documents, 5.35%), Taiwan (46 documents, 5.24%), Türkiye (37 documents, 4.21%), Australia (36 documents, 4.10%), Norway (33 documents, 3.76%), and South Korea (33 documents, 3.76%).

The VOSviewer program reveals that the USA leads in co-authorship among countries, with 331 documents and 5376 citations. Iran, England, and Brazil also show significant activity in co-authorship efforts. Türkiye and South Korea, though with fewer documents and citations, still participate in collaborative efforts. Iran has 70 documents and 927 citations, followed by England with 68 documents and 2315 citations. Brazil has 61 documents and 804 citations, and Canada rounds out the top five with 47 documents and 841 citations, demonstrating its significant role in fostering global research partnerships. According to the analysis using the VOSviewer program, the co-authorship analysis between countries is visualized in Figure 2. The visualization uses frame sizes to represent variation in publication counts among countries, and larger frames indicate greater disparity in publication counts. Color

Table 2. Most popular citation topics micro

Citation topics micro	n	% of 878
Spirituality	657	74.829
Palliative care	23	2.620
Cancer survivors	20	2.278
Nursing	20	2.278
Mindfulness	12	1.367
Job satisfaction	12	1.367
Dementia caregivers	8	0.911
Breech presentation	6	0.683
Childhood cancer	5	0.569
Bereavement	5	0.569
Peritoneal dialysis	4	0.456
PTSD	4	0.456
Autobiographical memory	4	0.456
Shared decision making	3	0.342
HIV prevalence and prophylaxis	3	0.342
Parapsychology	3	0.342
Rectal cancer	2	0.228
Breast cancer incidence	2	0.228
Self-rated health	2	0.228
Mycobacterium tuberculosis and leprosy	2	0.228
Suicide	2	0.228
Cardiac rehabilitation	2	0.228
Diabetes	2	0.228
Alternative medicine	2	0.228
Heart failure	2	0.228
Postpartum depression	2	0.228
Twin-twin transfusion syndrome	2	0.228
Homelessness	2	0.228
Subjective well-being	2	0.228

*20 record(s) (2.278%) do not contain data in the field being analysed. PTSD: Post-traumatic stress disorder, HIV: Human immunodeficiency virus.

Table 3. Top cited articles on spiritual healing-related literature in the nursing field

Title	Authors	Title of journal	DOI	Total citations	Average per year
An online survey of nurses' perceptions of spirituality and spiritual care	McSherry and Jamieson ²¹	Journal of Clinical Nursing	10.1111/j.1365-2702.2010.03547.x	179	12.79
Spiritual care in nursing: an overview of the research to date	Ross ²²	Journal of Clinical Nursing	10.1111/j.1365-2702.2006.01617.x	174	9.16
The crescent and Islam: healing, nursing and the spiritual dimension. Some considerations towards an understanding of the Islamic perspectives on caring	Rassool ²³	Journal of Advanced Nursing	10.1046/j.1365-2648.2000.01614.x	168	6.72
Spiritual care in nursing: a concept analysis	Ramezani et al. ²⁴	International Nursing Review	10.1111/inr.12099	153	13.91
The construct validity of a rating scale designed to assess spirituality and spiritual care	McSherry et al. ²⁵	International Journal of Nursing Studies	10.1016/S0020-7489(02)00014-7	146	6.35
A critical incident study of nurses' responses to the spiritual needs of their patients	Narayanasamy and Owens	Journal of Advanced Nursing	10.1046/j.1365-2648.2001.01690.x	145	6.04
The Spirituality scale development and psychometric testing of a holistic instrument to assess the human spiritual dimension	Delaney, Colleen	Journal of Holistic Nursing	10.1177/0898010105276180	132	6.6
Focus on spiritual well-being: Harmonious interconnectedness of mind-body-spirit - Use of the JAREL Spiritual Well-Being Scale - assessment of spiritual well-being is essential to the health of individuals	Hungelmann et al.	Geriatric Nursing	10.1016/S0197-4572(96)80238-2	127	4.38
Quality of life in breast cancer Part II: Psychological and spiritual well-being	Ferrell et al.	Cancer Nursing	10.1097/00002820-199802000-00001	124	4.59
Nursing competencies for spiritual care	Baldacchino, Donia R.	Journal of Clinical Nursing	10.1111/j.1365-2702.2006.01643.x	117	6.16
The validity and reliability of an instrument to assess nursing competencies in spiritual care	van Leeuwen et al.	Journal of Clinical Nursing	10.1111/j.1365-2702.2008.02594.x	116	7.25
Nursing competencies for spiritual care	van Leeuwen and Cusveller	Journal of Advanced Nursing	10.1111/j.1365-2648.2004.03192.x	115	5.48
Spiritual care: implications for nurses' professional responsibility	van Leeuwen et al.	Journal of Clinical Nursing	10.1111/j.1365-2702.2006.01615.x	101	5.32
Spiritual needs of patients with cancer and family caregivers	Taylor EJ	Cancer Nursing	10.1097/00002820-200308000-00002	100	4.55
Effect of spiritual intelligence, emotional intelligence, psychological ownership and burnout on caring behaviour of nurses: a cross-sectional study	Kaur et al.	Journal of Clinical Nursing	10.1111/jocn.12386	99	8.25
Spiritual health of oncology patients: nurse and patient perspectives	Highfield MF	Cancer Nursing	10.1097/00002820-199202000-00001	91	2.76
Student nurses perceptions of spirituality and competence in delivering spiritual care: a European pilot study	Ross et al.	Nurse Education Today	10.1016/j.nedt.2013.09.014	90	8.18
Spiritual care nursing: what cancer patients and family caregivers want	Taylor EJ, Mamier I	Journal of Advanced Nursing	10.1111/j.1365-2648.2004.03285.x	90	4.5
Dilemmas of spiritual assessment: considerations for nursing practice	McSherry and Ross	Journal of Advanced Nursing	10.1046/j.1365-2648.2002.02209.x	90	3.91
Spiritual aspects of nursing	Ross LA	Journal of Advanced Nursing	10.1111/j.1365-2648.1994.tb01105.x	90	2.9
The spiritual dimension: its importance to patients' health, well-being and quality of life and its implications for nursing practice	Ross L	International Journal of Nursing Studies	10.1016/0020-7489(95)00007-K	89	2.97
Attributes of spiritual care in nursing practice	Sawatzky and Pesut	Journal of Holistic Nursing	10.1177/0898010104272010	80	4
Spiritual activities as a resistance resource for women with human immunodeficiency virus	Sowell et al.	Nursing Research	10.1097/00006199-200003000-00003	79	3.16
Living in aged care: using spiritual reminiscence to enhance meaning in life for those with dementia	MacKinlay and Trevitt	International Journal of Mental Health Nursing	10.1111/j.1447-0349.2010.00684.x	78	5.2
The principal components model: a model for advancing spirituality and spiritual care within nursing and health care practice	McSherry, Wilfred	Journal of Clinical Nursing	10.1111/j.1365-2702.2006.01648.x	76	4

coding represents collaborative authorship, with nodes of the same color indicating partnerships. The edges, representing total link strength, illustrate the intensity of collaboration between countries. Stronger connections are represented by thicker, more prominent edges. This visualization technique provides a scientific approach to understanding publication counts, collaborative authorship relationships, and partnerships among nations.

Top Published Organisations

A total of 1098 organizations contributed to the literature on spiritual healing in nursing, and at least 59 of them had 5 or more articles. The detailed publication and citation counts of the top 10 institutions contributing to the literature on spiritual healing were as follows: Loma

Linda University with 34 publications and 720 citations, followed by the University of São Paulo with 21 publications and 505 citations. The University of Malta ranked third with 14 publications and 575 citations, while Staffordshire University ranked fourth with 13 publications and 543 citations. The Catholic University of Portugal had 13 publications and 155 citations, while Azusa Pacific University was in fifth place with 12 publications and 206 citations. Sahmyook University, Shaqra University, Case Western Reserve University, and Chang Gung University of Science and Technology ranked 12th with 12, 12, 11, and 11 publications respectively. The visual in Figure 3 visualizes the density visualization analysis of the top published organizations related to spiritual healing in nursing.

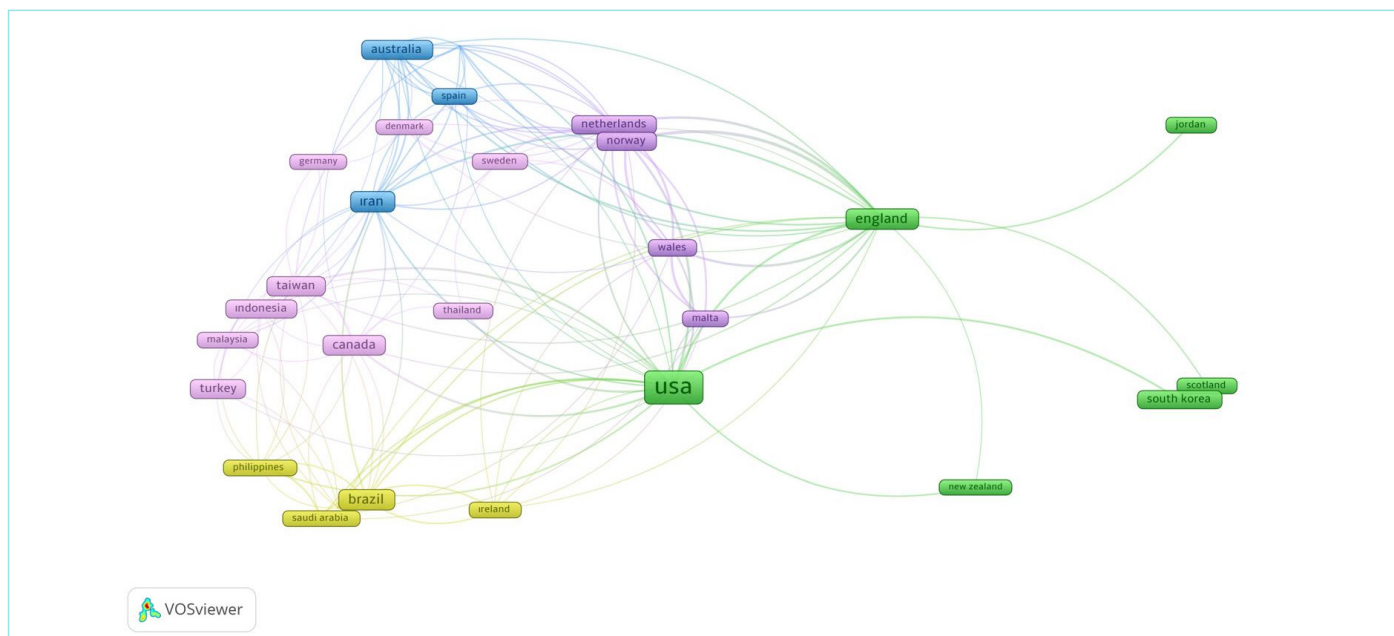


Figure 2. Co-authorship analysis between countries.

USA: United States of America.



Figure 3. Density visualization analysis between top published organizations.

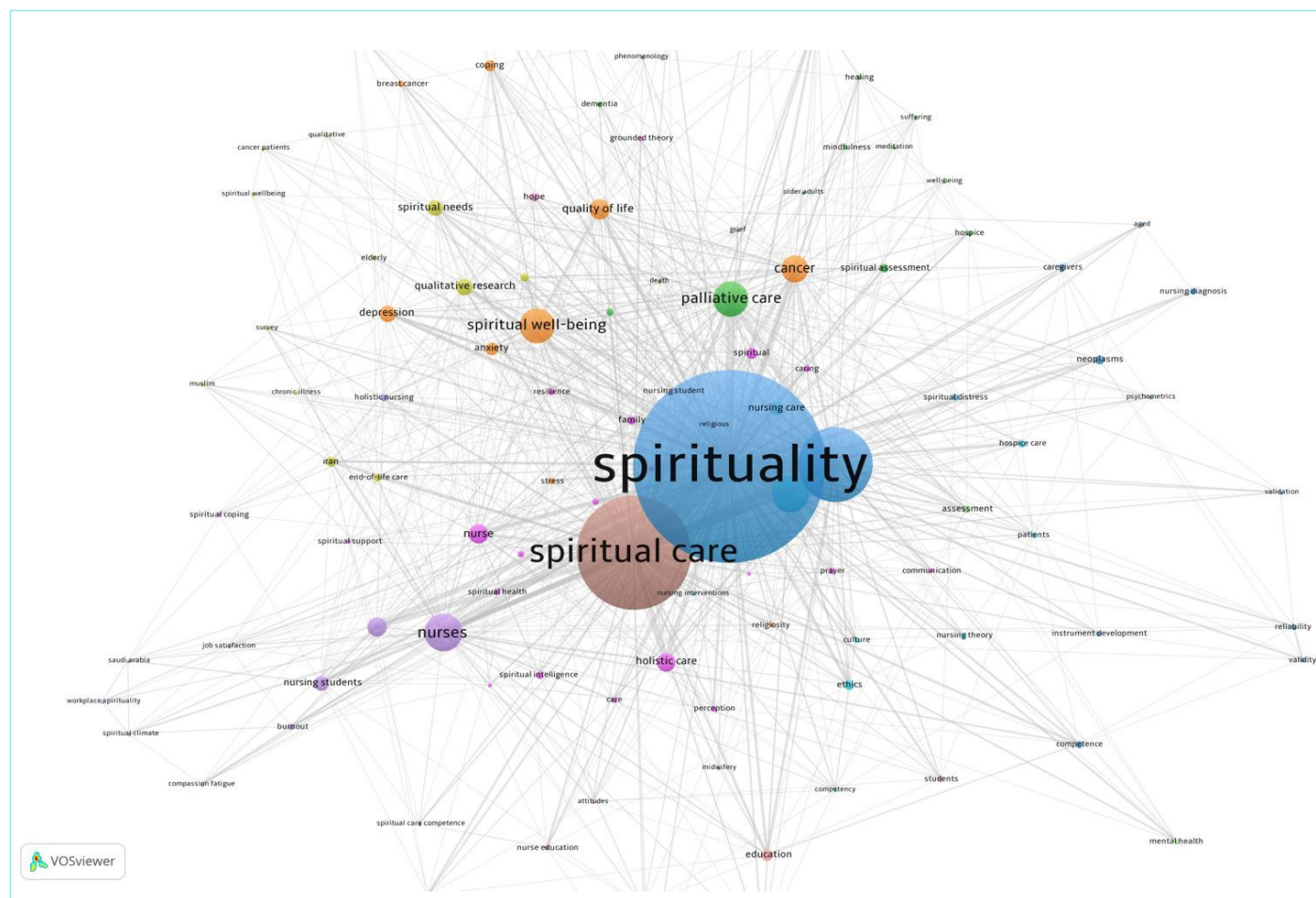


Figure 4. Keyword analysis.

Top Journals

A total of 146 journals published articles on spiritually themed nursing research. In the list of journals where the most publications, “Journal of Holistic Nursing” is the most productive journal writing 61 articles and citing them 1061 times. “Journal of Christian Nursing” followed, with 57 publications and 247 citations. Other significant inputs were “Journal of Clinical Nursing” publishing 50 articles and citing them 2179 times, and “Journal of Advanced Nursing”, with 47 documents and 1895 citations. The other journals include “Journal of Hospice and Palliative Nursing” were published 29 articles and used 163, “Nurse Education Today” they published 27 articles and cited them 963, and “International Journal of Palliative Nursing” they published 26 documents and quoted 306 one time. The names, the number of publications, and the number of citations of journals publishing the most articles are previously summarized in Table 4.

Top Themes

First of all, the analysis using VOSviewer helped to identify many keywords that are most often repeated and play an important role in the analysis results. These words include spirituality 405 times, spiritual care (226 times), nursing (140 times), nurses (66 times), religion (63 times), palliative care (61 times), spiritual well-being (61 times), cancer (44 times), quality of life (33 times), nurse (32 times), nursing education

(31 times), holistic care (30 times), depression (27 times), and qualitative research (27 times), spiritual needs (25 times), nursing students (23 times), nursing care (21 times), anxiety (20 times), and education (18 times). These words are often encountered in studies on spiritual and nursing topics, and therefore have an important role in the literature. In-depth analysis using the “topic modelling” text analysis method identified the main topics associated with the keywords. The analysis results reveal that the keywords, spirituality and spiritual care, define spiritual topics and issues in the care sphere, such as spiritual well-being and palliative care. Those such as nursing education are associated with topics on nursing education and care, such as nursing students, nursing care, and quality of life. Keywords like cancer and oncology are associated with topics related to cancer, while depression and anxiety are associated with psychological health. Thus, this analysis clarifies certain points in studies on spiritual and nursing topics (Figure 4).

DISCUSSION

Despite the growing importance of spirituality in the field of health, bibliometric analyses on this topic are rare.^{26,27} This is because spirituality is a complex and multifaceted concept that cuts across different disciplines. The lack of standardized terms and the personal nature of the topic also contribute to the paucity of such analyses. However, with spirituality becoming increasingly recognized in health, more bibliometric studies are needed to better understand research

Table 4. Top published journals

Journal	Number of documents	Number of citations
Journal of Holistic Nursing	61	1061
Journal of Christian Nursing	57	247
Journal of Clinical Nursing	50	2179
Journal of Advanced Nursing	47	1895
Journal of Hospice and Palliative Nursing	29	163
Nurse Education Today	27	963
International Journal of Palliative Nursing	26	306
Journal of Nursing Management	25	392
Holistic Nursing Practice	24	361
Cancer Nursing	22	589
Oncology Nursing Forum	18	490
Perspectives in Psychiatric Care	18	168
BMC Nursing	16	154
Revista Brasileira de Enfermagem	14	119
Iranian Journal of Nursing and Midwifery Research	12	28
Enfermería Clínica	11	12
Nursing Open	11	50
Western Journal of Nursing Research	11	309
Applied Nursing Research	10	247
European Journal of Cancer Care	10	212
Geriatric Nursing	10	256
International Journal of Nursing Studies	10	466
Journal of Korean Academy of Nursing	8	72
Journal of Nursing Research	8	146
Revista da Escola de Enfermagem da USP	8	73

in this area. As these intersections can be researched by scholars, we should expect an increasing amount of bibliometric research. The current bibliometric study has allowed the scrutiny of all spiritually themed works on the topic of nursing. Considering the above, search results from the Web of Science Core Collection database were filtered using the selected keywords to find published articles on the Web of Science platform. As a result, 878 articles relevant to nursing were obtained, although the inclusion of arbitrary selection criteria and varying proportions is noted. Publications on the topic of spirituality, relevant from the point of view of nursing, indicate an annual increase in articles. The number of publications appears to have increased significantly from year to year until 2016. The tendency to increase the number of literature on the topic of spiritual studies in nursing testifies to the increased importance and use of spirituality in nursing practice. Thus, spirituality as a need corresponding to a person's organism is increasingly performing a significant role, which demonstrates the importance of considering spirituality not only to account for the sensory feature of residents but also related medical and practical aspects of the treatment conflict.

We were mainly interested in spirituality research in the context of nursing. Demir²⁶ also conducted a bibliometric analysis of documents

about spirituality, religion, and health in general. However, since our works explored different subfields, the insights they provide appear unique. Demir²⁶ presented a more general picture, whereas our research centered on a more specific area. Demir's²⁶ research presents a bibliometric analysis of published documents on spirituality, religion and health. The research covered articles published between 1975 and 2017. A total of 1674 publications were found, of which 818 were articles. Between 1999 and 2013, a study showed that research in the field of spirituality and religion increased significantly.²⁷ This bibliometric analysis by Lucchetti and Lucchetti²⁷ revealed a marked increase in studies published in English, led by the USA and the United Kingdom (UK). Emerging countries such as India, Brazil, Israel and Iran have also made notable contributions to the field.

In Demir²⁶ study, the USA was identified as the most productive country, followed by the UK and Canada. Similarly, in our own study, the USA was found to be the largest contributor. However, in addition to these results, we also found that developing countries made significant contributions. For example, we found that countries such as Iran, Brazil, India, Saudi Arabia, and South Africa also contributed significantly to the literature. This suggests that participation in mental wellbeing research in nursing is widespread globally and is not limited to developed countries.

Citation analysis further illuminates key themes in the literature, highlighting the centrality of religion and its connection to palliative care. This highlights the profound impact of spiritual healing on end-of-life care, underscoring the importance of providing solace and support, especially to individuals struggling with terminal illnesses. Additionally, the analysis reveals the multifaceted nature of spiritual healing research in nursing by identifying micro-level issues such as mindfulness and job satisfaction. This detailed research encompasses multiple dimensions of human experience and well-being, reflecting the complexity of spiritual care.

Additionally, analysis of geographic distribution and collaboration across countries reveals a global collaborative effort to advance research on spiritual recovery in nursing. The leadership of countries such as the USA, Iran, the UK, and Brazil encourages cross-cultural dialogue and knowledge exchange, emphasizing the diverse and inclusive nature of this research environment. This global collaboration signals a shared commitment to exploring the intersection between spirituality and healthcare and transcends geographic boundaries to address universal human needs. Demir²⁶ reported that the country with the most publications was the USA (60.5%) and the most prolific journal was Journal of Religion and Health. The leadership of these countries may be based on different factors. The USA leadership role can be attributed to its extensive research infrastructure and access to funding sources, as well as its comprehensive universities and health systems. Iran's leadership position, along with its cultural and religious context, can be attributed to increased investments in health research and international cooperation efforts. The UK's leadership can be based on having a long history in healthcare and academia, and strong links to international research networks. Brazil's leadership position can be attributed to its large population and innovative approaches to healthcare. Canada's leadership role may be based on factors such as government support for health research and strong university-hospital collaborations. The leadership of these countries may reflect their emphasis on health research and particularly the field of spiritual healing, and their commitment to advancement in this field.

In total, 1098 organizations contributed to nursing literature in the field of spiritual recovery. Of these, there are 59 organizations have published at least five articles. These institutions are Loma Linda University (USA), University of São Paulo (Brazil), University of Malta (Malta), Staffordshire University (UK), Portuguese Catholic University (Portugal), Azusa Pacific University (USA), and Sahmyook University (South Korea). The institutions include Shaqra University (Saudi Arabia), Case Western Reserve University (USA), and Chang Gung University of Science and Technology (Taiwan). Loma Linda University ranks first with 34 publications and 720 citations, followed by the University of São Paulo, the University of Malta, the University of Staffordshire, and the Portuguese Catholic University. Reasons for these results may include factors such as the existence of universities' research centers or institutes focusing on spiritual healing, access to health systems in certain geographical regions, areas of expertise of researchers and academics, financial resources, research infrastructure, and international cooperation opportunities. In Demir²⁶ study, Duke University was identified as the top contributing institution, followed by the University of Michigan.²⁶ In our study, Loma Linda University stood out as the most productive institution, followed by the University of São Paulo. This shows that different universities are prominent in psychological recovery research in the field of nursing.

Most of the keywords mentioned in Demir's²⁶ study were similar to those in our study. Both studies emphasize that spiritual and religious issues are important for a healthy life. Nevertheless, such words as happiness, religious coping, adolescence, and health-related quality of life were not included in our study. However, the observed difference may be due to the variation in subtopics and the repetition of concepts in the studies. As for our study, the following keywords were mostly repeated: spirituality, spiritual care, nursing, religion, palliative care, and quality of life. These keywords indicate the main focus of the research and the role of spiritual care performed by the nurse in the context. Religion characterizes its general role and influences in health care. Palliative care describes the importance of the spiritual layer of care in the last stages of the disease, quality of life, and patients, and highlights the differences in health care in this aspect. However, words such as nurses, mental health, well-being, and happiness are central to the study's concept because the nurses' mental health, general health status, life satisfaction, and happiness are the analyzed measures. These keywords further describe the scope of the study and the wide range of mental care within the healthcare field.

Study Limitations

Limitations of this study include dependence on the Web of Science Core Collection search engine, which may exclude relevant publications that are not indexed in this database. Additionally, focusing solely on publications in English may have excluded valuable contributions in other languages, which may limit the comprehensiveness of the analysis. Additionally, it focused only on the field of nursing, and only articles were chosen as the document type. Additionally, although the use of bibliometric techniques may provide quantitative insights, they may not capture the nuanced qualitative aspects of spiritual healing research in nursing. Moreover, interpretation of results depends on the accuracy of keyword selection and clustering algorithms, which may neglect bias or emerging themes. Finally, the scope of the study was limited to articles specifically addressing spiritual healing in nursing, which may exclude related topics or interdisciplinary perspectives but still offer valuable insights into holistic care practices.

CONCLUSION

To conclude, the bibliometric analysis discussed in this paper presents several trends and contributions of spiritually themed articles in "nursing." Particularly, the trends show that spiritually-related issues began to be published starting in 2016. This may suggest that more holistic care provision, that is, including spiritual domains and satisfying patients' needs, became even more available. In terms of the research compass, the findings of this research address global collaboration in spirit medicine, including the most fruitful years (e.g., 2023), leading journals (e.g., *Journal of Holistic Nursing*), the leading institutions (e.g., Loma Linda University), and the leading country (e.g., USA).

It is important to better understand the issue of spiritual health and nursing care, as well as to reflect the obtained data on patient care. In this context, it is recommended to identify relevant literature, diversify data sources, utilize advanced statistical methods, and take into account international perspectives due to the cultural diversity of the spiritual approach. Additionally, ensure the use of continuously updated data and examine previous studies in depth, since thematic mapping is an indispensable part of the spiritual approach.

MAIN POINTS

- In recent years, spiritual healing has emerged as a significant aspect of holistic nursing care, addressing the spiritual dimensions of health and well-being.
- This bibliometric analysis aimed to shed light on important trends, research questions, and contributions within the academic literature on spiritual healing in nursing.
- In light of the information shared, it is important to see the rise and importance of the study of spiritual healing and its place in the nursing field.
- Analyzing the prominent countries, publications, citations, and their distribution will be an important resource to follow the developments in the field of spiritual care.
- The importance of spiritual healing in nursing care will be understood, and its place in health care systems will be emphasised more.

ETHICS

Ethics Committee Approval: Ethical approval is not required as this study does not involve human or animal subjects.

Informed Consent: This publication was made using a free database. It also did not require informed consent as it was a literature review without human and animal samples.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.Ö.A., H.A., H.G., G.G., Concept: H.Ö.A., H.A., H.G., G.G., Design: H.Ö.A., H.A., H.G., G.G., Data Collection and/or Processing: H.Ö.A., H.A., Analysis and/or Interpretation: H.Ö.A., H.A., Literature Search: H.Ö.A., H.A., H.G., G.G., Writing: H.Ö.A., H.A., H.G., G.G.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study had received no financial support.

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Non-Prescription Drug Use: Development of Antimicrobial Resistance

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Abstract

Antimicrobial resistance (AMR) is becoming a major health problem worldwide. Different factors contribute to the emergence of resistance, including excessive and inappropriate use of antibiotics. Non-prescribed antibiotic use is still widespread and contributes to antibiotic resistance. This study presents the development of drug resistance in a woman with recurrent urinary tract infection, highlighting the role of antibiotics taken without a prescription and emphasizing the importance of culture and antibiotic susceptibility tests in the success of treatment. In this case, inappropriate use of antibiotics triggered AMR, and consequently, the treatment has failed. An effective medication management system is necessary to monitor non-prescription antibiotic use in North Cyprus. Raising public awareness through education programs can reduce inappropriate and excessive antibiotic use. The development of resistance to commonly used antibiotics also reveals the need to develop new treatment strategies in the country.

Keywords: Antibiotic resistance, antibiotic susceptibility testing, infectious disease, non-prescription drugs

INTRODUCTION

Antimicrobial resistance (AMR) is becoming a major global threat in all countries due to the excessive and unregulated use of antibiotics.¹ In 2019, there were 4.95 million deaths worldwide due to AMR, of which 1.27 million were associated with AMR.² Additionally, uncontrolled and unscientific use of antimicrobials in livestock contributes to the emergence of resistant pathogens.³ AMR means that microorganisms causing bacterial, viral, fungal, and parasitic infections have developed resistance and cannot be killed by the drugs meant to treat these infections.³ Due to the emergence of drug-resistant pathogens and difficulties in treating widespread bacterial infections, vital procedures such as surgery, organ transplantation, and cancer treatments, etc. are also becoming increasingly risky.² Additionally, the coronavirus disease-2019 (COVID-19) pandemic has contributed to the silent

spread of AMR recently due to the widespread overuse of antibiotics for severe and hospitalized patients.⁴ The World Health Organisation (WHO) reported that only 8% of hospitalized COVID-19 patients required antibiotic treatment due to bacterial co-infection while, 75% of the remaining were treated to prevent possible bacterial co-infections, leading to unnecessary antibiotic use. Between 2020 and 2022, the rate of antibiotic consumption rose from 33% to 83%, especially in the Eastern Mediterranean and the African regions, while decreasing in Europe and the Americas over time.^{4,5}

The WHO's Global Antimicrobial Resistance Surveillance Report revealed AMR mainly in *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella* spp., *Acinetobacter* spp., *Staphylococcus aureus*, *Neisseria gonorrhoea*, and *Streptococcus pneumoniae*, in regions of Africa, the Americas, South East Asian, European, Eastern Mediterranean,

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and Western Pacific.⁶ The rise in resistance of third-generation cephalosporin-resistant *E. coli*, methicillin-resistant *S. aureus*, and the reduced susceptibility of *E. coli* to commonly prescribed antibiotics, including ampicillin, co-trimoxazole, and fluoroquinolones, in urinary tract infections (UTIs), poses a significant concern.² Moreover, decreased susceptibility of *K. pneumoniae* to critically important drugs complicates treatment management. Increasing levels of resistance potentially lead to increased use of last-choice drugs such as carbapenems, and when the efficacy of these last-choice drugs is compromised, the risk of untreatable infections increases.² Additionally, there is a growing concern about resistance to antiviral drugs used in the treatment of human immunodeficiency virus, multidrug resistance to isoniazid and rifampin in tuberculosis, partial resistance to artemisinin in *Plasmodium falciparum* infections, resistance to rifampin and clofazimine in leprosy infections, resistance to melarsoprol for trypanosomiasis, and resistance to pentavalent antimonials and miltefosine for leishmaniasis.

This study examines the development of drug resistance in women with UTI due to non-prescription antibiotic use and highlights the importance of performing urine culture and antibiotic susceptibility tests for treatment success.

CASE REPORT

A 41-year-old female patient was admitted to the microbiology laboratory with recurrent urinary tract symptoms, including pain and burning during frequent urination; foul-smelling cloudy urine; pain in her back; and hematuria. The initial symptoms started at the beginning of July 2024, while traveling to Bali, Indonesia, from North Cyprus. During a 13-hour plane trip, the patient experienced difficulty due to excessive water intake and was unable to urinate properly. Due to the sudden onset of the similar symptoms mentioned above, the patient used fosfomycin for two doses 3 days apart, without admitting to a hospital and performing a urine culture test. As she felt recovered, a microscopic urinalysis test and urine culture were not performed after she came back to her country. In mid-August 2024, the same symptoms recurred. During another summer vacation when the symptoms started, the patient could not access a clinic to have a urine culture performed again. Therefore, she used a cefuroxime film tablet every 12 hours for 5 days without a doctor's prescription. On the second day, she felt better, and the symptoms regressed. However, she did not feel fully recovered on the fifth day of the treatment. Consequently, she was admitted to a hospital and performed urine microscopy and culture tests two days after the antibiotic treatment. In her cloudy light yellow urine, nitrite positivity, strong leukocyte positivity, and trace blood positivity were reported in the urine strip test. In microscopic urinalysis, plenty of leukocytes, 4-6 erythrocytes, sparse squamous epithelium cells, and plenty of bacteria were detected. After 24 hours of incubation, growth was detected on the blood agar and eosin methylene blue (EMB) agar (>100.000 CFU/mL). Microbial identification and antibiotic susceptibility testing were performed using the VITEK2 (Biomerieux) automated system and evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria.⁷ According to the analysis, extended-spectrum beta-lactamase (ESBL) producing *E. coli* was reported in the urine culture. The detected pathogen was resistant to amoxicillin/clavulanate, ampicillin, cefepime, ceftazidime, ceftriaxone, cefuroxime-axetil, ciprofloxacin, piperacillin/tazobactam and trimethoprim/sulfamethoxazole. Susceptibility was detected for

amikacin, ceftiofur, cefixime, ertapenem, gentamicin, meropenem, and nitrofurantoin. A cefixime tablet every 24 hours for 5 days was prescribed for the case. After 5 days of treatment, microscopic urinalysis and urine culture with the same techniques were repeated and the results were reported as negative.

Although there was no vaginal odor, itching, burning, or pain, a vaginal culture was also taken because of the slight vaginal discharge and the possibility of contamination due to UTI. A vaginal fresh smear, gram staining, culture, and A.F. genital system (Liofilchem, Italy) were performed to identify vaginal pathogens. The vaginal swab sample was inoculated on blood and EMB agars and incubated for 24-48 hours at 36 °C. Bacterial identification and antibiotic resistance patterns were determined with the VITEK2 (Biomerieux) automated system according to EUCAST guidelines.⁷ In the vaginal fresh smear, 9-10 vaginal epithelial cells, increased leukocytosis, and bacteria were reported. In Gram staining, gram-negative bacilli were detected, while Döderlein's vaginal bacilli disappeared in the flora. Clue cells, gram (+)/(-) cocci, gram (+)/(-) bacilli, gram (-) diplococci, *Candida* spp, and *Trichomonas vaginalis*, were not detected in gram staining. Additionally, *Ureaplasma* spp. and *Mycoplasma hominis* were not detected in the A.F. genital system. In the vaginal culture, *E. coli* ESBL was identified. The isolate was found to be resistant to cefixime, amoxicillin, amoxicillin/clavulanate, gentamicin, amikacin, ceftriaxone, and cefuroxime, while susceptible to ciprofloxacin and norfloxacin, and susceptible to ampicillin/sulbactam, trimethoprim/sulfamethazole, and ofloxacin. The patient was prescribed ampicillin + sulbactam every 12 hours for 5 days. As prophylaxis, tioconazole (200 mg), tinidazole (300 mg), and lidocaine (100 mg) vaginal ovule were used for 3 days (1x1) to prevent fungal infections. Moreover, *Lactobacillus acidophilus* (100 million) and estriol (0.03 mg) vaginal tablets were used for 6 days for renewal of flora. The patient recovered after treatment without developing any complications.

DISCUSSION

AMR is a growing health problem worldwide, affecting the sectors of human health, food production, animal, and environment. In 2015, WHO released the Global Action Plan on AMR, which includes developing and implementing multisectoral action plans, raising awareness, increasing surveillance and data, reducing infection rates, ensuring safe and effective use of antimicrobials, and developing new treatment strategies and alternatives,⁸ in North Cyprus, dispensing non-prescription antibiotics has been prohibited since April 1, 2016. Although the law is now in force in North Cyprus, there is no effective monitoring system for users and healthcare systems.⁹ Drug tracking and e-prescription systems, modern technologies required for health services, were planned in North Cyprus but could not be implemented. These systems should be implemented urgently to cover all public and private physicians, pharmacies, and pharmaceutical warehouses.¹⁰ In this case, the patient was able to purchase medication without a prescription during travel abroad, and, when she felt unwell, she preferred self-medication. Since her complaints recurred within a month and coincided with her next vacation, she repeated the use of non-prescription antibiotics, which contributed to the development of resistance. Various factors such as lack of time to perform antibiotic susceptibility testing, as in this case, lack of awareness or education, and inadequate access to healthcare systems during disasters may contribute to the development of antibiotic resistance globally. Unal Evren et al.¹¹ reported increased ESBL positivity among

uropathogens during COVID-19 in North Cyprus. The decrease in the rate of pandemic period admissions was reported as a possible contributing factor to this result.¹¹ The detection of ESBL positivity in untreated cases due to inappropriate antibiotic use and the detection of ESBL in approximately 30% of travelers, highlights the need for antibiotic susceptibility testing and the importance of appropriate antibiotic use for treatment success.¹²

Countries where self-medication is widespread and uncontrolled, are triggering AMR and also leading to high costs and side effects resulting from long-term treatment failure. Using antibiotics without a prescription is more generally reported in low-income countries than in high-income countries.¹³ Many factors contribute to this approach, including traveling abroad, lack of education among the population and even among pharmacy staff, expensive or difficult access to healthcare services, and lack of healthcare insurance.¹²⁻¹⁵ According to the survey-based studies on non-prescription drug use and sales in North Cyprus in 2014, Sürer et al.⁹ revealed that 97.5% of pharmacies in different cities in North Cyprus answered “yes” to whether they sell medicines without a prescription. In another study conducted on the population, it was determined that 87% of people have used non-prescription drugs at least once in their lives.¹⁶ In those years, The high rates of drug sales and purchases without complying with the rules in North Cyprus showed that a regulatory intervention was necessary. In recent studies, antibiotic consumption and use without a medical prescription were reported at 43.8%, 45%, and 47% in different regions in the United States and some low and middle-income countries.^{17,18} In a systematic review, the prevalence of non-prescription antibiotic dispensing from community pharmacies reached 63.4%, with the highest rates in sub-Saharan Africa, East Asia, and the Pacific, Latin America, and the Caribbean.¹⁹ In a similar study conducted by Gravningen et al.¹⁵ between 2015-2016, Thailand, Türkiye, and Spain had the highest rates of purchasing antibiotics without a prescription (10.7%, 5.5%, and 3.6%, respectively). The prevalence of antibiotic dispensing without a medical order remains high in other countries (63.1%). The study revealed that the most common antibiotics sold without a valid prescription in China were cephalosporins (44.1%) and amoxicillin (39.0%).²⁰

To combat the emergence of AMR, it is important to raise awareness among the public and health workers and to carry out effective inspections to prevent the purchase of medications without a prescription. Our case highlights that using antibiotics without a prescription contributes to antibiotic resistance and reduces treatment success. Antibiotic susceptibility testing is critical for determining the most appropriate treatment option and improving success.

CONCLUSION

In conclusion, insufficient monitoring of non-prescription antibiotic use and selling in North Cyprus triggers antibiotic resistance. Raising public awareness through educational programs can reduce inappropriate and excessive antibiotic use. The development of resistance to basic antibiotics also reveals the necessity of developing alternative therapeutic approaches.

MAIN POINTS

- Inappropriate antibiotic use may have contributed to antimicrobial resistance in North Cyprus.

- Culture and antibiotic susceptibility testing should be performed before prescribing antibiotics, to reduce antibiotic resistance.
- An effective monitoring system for users and health systems should be implemented to reduce inappropriate antimicrobial use in North Cyprus.

ETHICS

Informed Consent: The consent form was obtained for the case.

Footnotes

Authorship Contributions

Concept: A.A., Design: A.A., K.S., Data Collection and/or Processing: A.A., K.S., Analysis and/or Interpretation: A.A., K.S., Literature Search: A.A., K.S., Writing: A.A.

DISCLOSURES

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