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Welcome to the first issue of the Journal of Emerging Minds in Undergraduate Research.

JEMUR began with a simple belief: students should have the opportunity to share their research, improve it through thoughtful feedback, and become visible members of the scientific community. Valuable ideas do not suddenly appear after graduation. They often begin much earlier—in a classroom discussion, a laboratory, an archive, a student project, or a question that someone decides to pursue seriously.

Reaching this first issue has been both exciting and demanding. Behind every published page are many conversations, careful readings, revisions, checks, and decisions. We have learned alongside our authors and reviewers throughout this process. Seeing the journal move from an idea to a completed issue has made all that work worthwhile.

We would first like to thank the student authors who trusted JEMUR with their research. They responded patiently to feedback, returned to their manuscripts several times, and showed a genuine willingness to improve their work. Their effort gives this journal its purpose.

We are equally grateful to our reviewers. They gave their time and expertise generously, approaching each manuscript with care and respect. Their detailed feedback helped our authors strengthen their arguments, clarify their methods, and present their work more confidently. The quality of this first issue owes a great deal to their contribution.

We also thank the colleagues, students, friends, and supporters who encouraged us during the journal's preparation. Establishing a new journal involves a great deal of work that readers may never see. Every message of encouragement and every practical contribution helped us move forward.

We hope JEMUR becomes a welcoming place for emerging researchers from different disciplines, institutions, and countries. We want students to feel that their questions matter and that careful research deserves to be read. We also hope this journal encourages them to remain curious, accept constructive criticism, and develop the confidence to participate in academic life.

This first issue is only the beginning. Thank you for being here at the beginning with us.

*Kadir Demir & Mehmetcan Erduran*

EDITOR-IN-CHIEF

EDITOR

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EDITORIAL

A Home for Emerging Minds: Welcome to JEMUR's First Issue

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ABSTRACT

This editorial welcomes readers to the first issue of the *Journal of Emerging Minds in Undergraduate Research*. We founded JEMUR as an international home where undergraduate and graduate students can make their work visible, receive serious feedback, and take an active place in the scientific community. That mission depends on careful publishing. Before external review, every manuscript in this issue underwent a citation and reference check. After editorial approval, two independent reviewers were assigned through a double-anonymous process. Two papers completed three review rounds and three completed two, giving the issue twelve external review rounds in total. Every paper also received at least two editorial evaluations. We introduce five studies that move across gender politics, visual culture, public-service training, cancer prevention, and targeted drug delivery. Together, they show how student research can speak to social, cultural, and health questions with care. We also consider what support should look like in the age of artificial intelligence. Clear guidance on responsible AI use, self-regulated learning, and opportunities beyond the classroom can help students become more thoughtful and independent researchers. For JEMUR, publication is part of education: a shared process of asking, checking, revising, and learning.

**Keywords:** student research; peer review; artificial intelligence; self-regulated learning; undergraduate research

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## 1. Introduction

We write these lines on a summer day, in the shade of a tree in Miletus — a birthplace of philosophy, science, and art by a curious coincidence. The systematic search for understanding that the Milesian School kindled in the sixth century BCE continues today through the tools of modern science and technology. Like researchers everywhere who wish to contribute to that search, we hope to support young scholars, especially at the start of their careers.

The *Journal of Emerging Minds in Undergraduate Research* (JEMUR) moves from an idea into a shared scholarly space with this first issue. We founded JEMUR because undergraduate and graduate students often do serious work long before they become visible members of the research community. A thesis chapter, laboratory project, archive search, community study, or carefully developed review may contain a real contribution, yet finding an international place to publish it can be difficult. JEMUR gives this work a permanent, accessible, and citable home.

That aim shapes how we think about international visibility. Scopus and TR Dizin, two of the leading scientific indexing databases, are long-term destinations for the journal. Reaching them requires steady editorial work: clear policies, reliable metadata, transparent ethics, careful peer review, and articles that readers can trust. We want students to be present in the scientific world through work that can be found, read, questioned, and cited. Visibility is earned one carefully prepared paper at a time.

## 2. Review as Part of Learning

Student authors deserve the same seriousness given to established researchers. Before external review, the editorial team examined every manuscript's citation and reference one by one. We checked whether in-text citations appeared in the reference list, whether details were complete and traceable, and, where questions arose, whether a source supported the surrounding claim. This protects the scholarly record and teaches that references are part of the evidence.

After editorial approval, every paper was assigned to two independent reviewers in a double-anonymous process. Two papers completed three review rounds and three papers completed two. Together, they passed through twelve external review rounds. Each paper also received at least two editorial evaluations, amounting to at least ten across the issue. Every round asked the authors to read closely, return to their evidence, make decisions, and improve the manuscript.

Our reviewers worked with remarkable care. Their reports were detailed, respectful, and focused on stronger research. For us, review is both quality control and mentoring. High standards become educational when feedback explains what needs attention and gives an emerging researcher a fair chance to respond. We thank every reviewer who gave time and expertise to this issue.

## 3. Five Papers, Many Directions

The five papers move across feminist political theory, visual culture, public-service training, cancer biology, and targeted drug delivery. Each begins with the same scholarly habit: looking carefully at a problem and asking what can be understood more clearly.

İrem Tabirlioğlu returns to Simone de Beauvoir's idea of woman as the "Other" and asks what it can still tell us about gender politics. Through cases from Iran and Afghanistan to algorithmic

discrimination and platform culture, she shows how patriarchal power can change its tools while preserving underlying patterns of inequality. Her Contemporary Otherness Framework connects existential feminism with the digital age.

Deniz Altıok Erduran studies how nine Turkish newspapers turned Galatasaray's 2000 UEFA Cup victory into twelve different front pages. Her reading of typography, color, photographs, and page position shows that layout is itself an editorial argument: a supporters' poster, a national celebration, or a more critical record. She also identifies formal echoes between late-analog pages and today's social-media sports graphics.

Kağan Gümüş and Emre Ünlü ask whether public-service personnel feel ready to serve autistic citizens and what training they would find useful. Among 115 participants in İzmir, self-perceived knowledge was low, especially regarding legal rights, while attitudes were more positive than preparedness. Only 25.2% felt prepared. Preferences for visual, applied, and relatively short training point toward practical, scenario-based learning.

İrem Kumru Öz reviews plant-derived compounds and propolis as possible multi-target agents in cancer prevention and progression. She maps their roles across apoptosis, metastasis, redox balance, and the tumor microenvironment while keeping clinical barriers in view, including bioavailability, interactions, standardization, and limited translation to reliable therapies.

Buket Küçükaslan, Emine Tatlı, Esmahatun Eser, Mislina Oğultarkan, and Gizem Kaleli Can examine hydroxyapatite microspheres for more selective treatment of HER2-positive breast cancer. They distinguish trastuzumab as controlled therapeutic cargo or a surface-bound targeting ligand and consider folic-acid functionalization. Antibody stability, reproducible production, in vivo testing, scale-up, and clinical validation remain open challenges.

#### **4. Learning in the Age of AI**

Artificial intelligence is already part of students' academic lives. In a recent survey of 1,054 full-time UK undergraduates, 95% reported using AI in at least one way, while fewer than half felt that teaching staff were helping them develop the skills they would need (Stephenson & Armstrong, 2026). One national survey cannot describe every context, but it illustrates how quickly practice can move ahead of guidance.

JEMUR responds through clear expectations and constructive feedback. Authors should state which tools they used, why they used them, and how they checked the results. Their argument, evidence, wording, citations, and ethical choices remain a human responsibility. Responsible use requires transparency, accountability, fairness, privacy, and meaningful human oversight (Erduran, 2025).

Self-regulated learning offers a practical frame. Students set goals, monitor understanding, seek feedback, and evaluate what they have produced. Anders and Dux Speltz (2025) connect AI literacy with a Plan-Iterate-Evaluate cycle that keeps learner agency visible: decide what a tool should do, inspect and improve its output, then reflect on the result and the process. Peer review follows a similar rhythm as authors plan an argument, reconsider it through evidence and feedback, and evaluate the revision.

## 5. Beyond the Classroom

Learning also needs space outside formal courses. Research groups, laboratories, student societies, archives, community projects, internships, and journals can help students discover that their questions matter. In a 2025 study of 4,473 undergraduate and graduate students in the Netherlands, extracurricular involvement was associated with stronger belonging and authenticity (Verbree et al., 2025). JEMUR aims to be one such space, bringing students into an academic community through researching, writing, revising, and publishing.

Publication becomes another stage of education. Authors learn to make claims carefully, document sources, work with collaborators, answer difficult questions, and revise repeatedly. This issue shows learning moving from the classroom into politics, media, public services, laboratories, and health research, then returning as knowledge that others can examine.

## 6. Looking Ahead

This issue belongs to its authors, reviewers, editors, and everyone who supported the work behind its pages. We will continue to build JEMUR through rigorous review, honest guidance, responsible use of technology, and wider visibility for student research. To students reading: begin with a question that matters, check every source, invite criticism, and revise with care. We are grateful to everyone who made this first issue possible, and we look forward to the questions students will ask next.

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RESEARCH ARTICLE

Simone de Beauvoir's Concept of Otherness and Contemporary Gender Politics: An Existential Feminist Perspective

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ABSTRACT

Since its publication in 1949, Simone de Beauvoir's *The Second Sex* has remained one of the foundational works of feminist thought, profoundly shaping debates on gender, freedom, and social inequality. Although Beauvoir's existential feminism has been widely examined within twentieth-century feminist theory, limited attention has been paid to its analytical relevance for understanding contemporary forms of institutional and technological patriarchy. This article examines the extent to which Beauvoir's concepts of otherness, freedom, immanence, transcendence, and anti-essentialism remain applicable to twenty-first-century gender politics. Employing an interpretive qualitative research design and a comparative case study approach, the study analyses four institutional contexts: the legal regulation of women's bodily autonomy in Iran following Mahsa Amini's death in custody, the systematic exclusion of women under Taliban rule in Afghanistan, algorithmic discrimination in artificial intelligence (AI) systems, and gender inequalities reproduced through digital platforms. Building on Beauvoir's existential philosophy and engaging with contemporary feminist scholarship—including Butler's theory of gender performativity, Crenshaw's intersectionality, recognition theory, and digital feminism—the article develops the Contemporary Otherness Framework (COF) as an integrative analytical model. Rather than arguing that patriarchal domination has disappeared through modernization and digitalization, the study demonstrates how it has adapted to new political, legal, and technological conditions. The findings suggest that while the institutional forms of gender inequality have evolved, the underlying dynamics of otherness, unequal recognition, and constrained freedom identified by Beauvoir continue to shape women's experiences. By bridging existential feminism with contemporary debates on digital governance and AI, the article contributes to feminist political theory and provides a comparative framework for analysing the evolving institutional architecture of patriarchal power in the digital age.

**Keywords:** Simone de Beauvoir; existential feminism; digital patriarchy; artificial intelligence (AI); Contemporary Otherness Framework (COF)

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## 1. Introduction

Ever since the publication of the book *The Second Sex* in 1949, Simone de Beauvoir has remained one of the most influential figures in feminist branch of political thought and existentialist philosophy. Her works on women's oppression fundamentally transformed the study of gender and discipline of gender studies by criticizing biological determinism and stating that femininity is not a fixed condition but a socially constructed identity shaped through historical, political, and cultural processes. Beauvoir's famous assertion that "one is not born, but rather becomes, a woman" has become one of the most frequently used statements in feminist school of thought, providing the basis for debates on gender construction, subjectivity, embodiment, and social inequality (Beauvoir, 2011, p.283). Even after seven decades passed from its publication date, *The Second Sex* continues to shape discussions over gender politics, illustrating the relevance of Beauvoir's existential feminist ideas in grasping the structural mechanisms through which patriarchal societies reproduce inequality.

Unlike earlier approaches that explained women's condition through biological or theological arguments, Beauvoir argued gender inequality is rooted within the broader existential condition of human existence (Beauvoir, 2011, p. 25). Drawing upon existential phenomenology and engaging critically with the philosophical traditions of Hegel and Sartre (Moi, 1999, p.60), she conceptualized women as the "Other," stating that patriarchal societies establish men as the universal and autonomous subject while women to a secondary and dependent position (Beauvoir, 2011, p. 6). Within this framework, women are not naturally inferior; rather, they become subordinated through historical institutions, cultural norms, and social practices that construct men as the normative subject and women as the "Other" (Beauvoir, 2011, p. 6). Consequently, Beauvoir redirected feminist inquiry away from biological essentialism toward an existential analysis of freedom, oppression, and social construction, an approach that later became a milestone for existentialist feminism (Moi, 1999, p. 60).

The importance of Beauvoir's theoretical contribution to the field extends even further beyond the 20th -century debates on women's emancipation process. Modern societies continue to witness persistent forms of gender inequality and gender-based oppression through discrimination, despite remarkable legal, political, and economic progress in many parts of the world. Gender-based violence, discriminatory labour markets, unequal political representation, and restrictions on reproductive rights continue to demonstrate the resilience of structural gender inequalities (Fraser, 2022, p. 5). Meanwhile, online harassment, algorithmic discrimination, and the commercialization of women's bodies through digital platforms reveal how patriarchy has adapted to emerging technological sphere (UN Women, 2023).

Against this background, this study seeks to reinterpret Simone de Beauvoir's theory of otherness through the perspective of modern gender politics by integrating existential feminist theory with current developments in feminist political thought and digital society studies. Rather than treating Beauvoir's work only as a historical milestone in feminism, this study aims to illustrate that her philosophy continues to provide a strong analytical basis for understanding the persistence and transformation of patriarchy in modern societies. To achieve this objective, the article addresses the following research questions: First research question seeks to answer to what extent does Beauvoir's concept of "the Other" remain relevant for explaining contemporary forms of gender inequality? Second, how can Beauvoir's concepts of freedom,

transcendence, and immanence be reinterpreted in light of contemporary debates on digital patriarchy and gender politics?

Rather than testing predetermined hypotheses, this article seeks to develop an interpretive framework that connects Beauvoir's existential feminism with contemporary debates on gender inequality. Accordingly, the analysis is organized around three interrelated objectives. First, it examines whether Beauvoir's concept of otherness continues to provide a meaningful analytical perspective for understanding the persistence of gender inequality in contemporary societies. Second, it explores how emerging forms of digital patriarchy—including algorithmic governance, artificial intelligence, and platform economies—can be interpreted through Beauvoir's concepts of freedom, immanence, and transcendence. Third, it assesses the extent to which integrating Beauvoir's existential feminism with contemporary feminist theories contributes to a more comprehensive understanding of twenty-first-century gender politics.

## **2. Methodology**

This study adopts a qualitative research design grounded in interpretive political theory and a comparative case study approach. Rather than testing causal hypotheses, the research seeks to interpret Simone de Beauvoir's existential feminist framework and examine the extent to which its central concepts remain analytically relevant for understanding contemporary forms of gender inequality across different institutional settings. Interpretive political theory is particularly appropriate for this purpose because it emphasizes the analysis of political ideas, meanings, and normative assumptions rather than the identification of causal relationships through hypothesis testing (Bevir & Rhodes, 2003; Schwartz-Shea & Yanow, 2012).

The research employs a comparative case study design to explore how patriarchal power is reproduced under diverse political, legal, and technological conditions. The empirical analysis focuses on four illustrative cases: the Mahsa Amini protests in Iran, restrictions on women's rights under the Taliban regime in Afghanistan, algorithmic discrimination and AI-enabled gender inequality, and platform economies associated with digital visibility and aesthetic labour. These cases were selected through purposive sampling because they represent distinct institutional configurations of gender inequality while enabling systematic comparison across different contexts (Flyvbjerg, 2006). Rather than seeking statistical generalization, the selected cases provide analytically rich examples that facilitate theoretical interpretation and comparison.

The study relies exclusively on qualitative data derived from primary and secondary sources. Primary sources include Simone de Beauvoir's *The Second Sex*, together with legal documents, reports, and policy publications produced by international organizations concerning women's rights, digital governance, and artificial intelligence. Secondary sources consist of peer-reviewed scholarship in feminist political theory, existential philosophy, intersectionality, digital governance, artificial intelligence, and gender studies. Since the objective is conceptual interpretation rather than empirical measurement, the study does not generate original data through interviews, surveys, or quantitative techniques.

The analytical process proceeds in three interconnected stages. First, Beauvoir's principal concepts—including otherness, freedom, immanence, transcendence, and anti-essentialism—are reconstructed through conceptual analysis. Second, these concepts are critically examined

alongside contemporary feminist scholarship on intersectionality, recognition theory, digital patriarchy, and algorithmic governance in order to identify both theoretical continuities and conceptual developments. Third, the proposed Contemporary Otherness Framework (COF) is comparatively applied to the selected case studies to examine how different institutional settings produce distinct configurations of patriarchal domination. Rather than assuming that the same mechanisms operate uniformly across all cases, the framework identifies which of its five analytical dimensions become dominant within each context, thereby enabling systematic comparison while preserving contextual specificity.

The comparative application of the COF also defines the scope of the framework. The model is intended to analyse institutionalized forms of gender inequality reproduced through political, legal, economic, and technological structures. It does not seek to provide a universal explanation for all manifestations of gendered experience or to replace context-specific analyses of culture, religion, ethnicity, or local historical conditions. Instead, these contextual factors are treated as variables that shape the institutional expression of patriarchal domination across different cases. Accordingly, the COF functions as a comparative interpretive framework that explains variation in the institutional reproduction of gender inequality rather than proposing a deterministic theory applicable to all societies.

### **3. Theoretical Analysis**

The rise of existential feminism cannot be understood independently from the philosophical tradition of existentialism that developed throughout the 19th and 20th centuries. Rejecting rationalist and essentialist human nature concepts, existentialism states that individuals are not born with predetermined identities or purposes but create themselves through freedom, choice, and responsibility. Its central premise—that existence precedes essence—places human beings in a condition of radical freedom while simultaneously imposing ethical responsibility for their actions (Sartre, 2007, p. 24).

Among existentialism's foundations, Søren Kierkegaard emphasized subjectivity, individual choice, and personal responsibility concepts in opposition to abstract philosophical systems (Kierkegaard, 1985, p.40). Martin Heidegger further developed this tradition by introducing the concept of *Dasein*, stating that human existence is situated within historical and social contexts rather than existing as an isolated rational consciousness (Heidegger, 1962, p.80). These philosophical developments eventually influenced Jean-Paul Sartre, who reformulated existentialism around the idea that freedom is the defining condition of human existence and that individuals are responsible for creating meaning through their choices (Sartre, 2007, p. 27).

Building upon this tradition, Simone de Beauvoir transformed existential philosophy into a critical framework for analysing systemic gender inequality. While Sartre mainly examined freedom as an individual existential condition, Beauvoir demonstrated that freedom is also shaped and constrained by social institutions and unequal power relations. Rather than simply applying Sartrean existentialism to women's condition, she reconceptualized freedom through the realities of embodiment, social oppression, and gendered subjectivity, thereby establishing the theoretical foundations of existential feminism (Moi, 1999, p.60). As Kruks (1990, p. 87) argues, Beauvoir should therefore be understood not as a follower of Sartre but as an independent theoretician whose reinterpretation of existentialism fundamentally transformed

feminist theory. Ever since the publication of *The Second Sex*, Simone de Beauvoir had a central position in feminist philosophy, political theory, and gender studies. Challenging essentialist understandings of gender and determinist school of thought, Beauvoir stated that femininity is not biologically predetermined but historically and socio-politically constructed, thereby shifting feminist scholarship from biological explanations of women's subordination toward an analysis of the political, cultural, and institutional mechanisms through which gender inequality is reproduced. Consequently, *The Second Sex* is widely regarded as one of the founding texts of modern feminist theory (Simons, 1999, p.2).

Beauvoir's anti-essentialist point of view has influenced feminist theory. Butler (1990, p.25) extended Beauvoir's arguments by conceptualizing gender as a performativity repeatedly produced through continuous social practices. While Beauvoir stated that femininity is socially produced rather than biologically predetermined, Butler further radicalized this argument by suggesting that gender itself is continuously constituted through the repetition of social performances rather than expressing any pre-existing identity (Butler, 1990, p.25). In Butler's words, gender is not something individuals possess but something they repeatedly enact within socially regulated norms through performativity (Butler, 1990, p. 25). Although Butler occasionally distances her work from existentialism, numerous scholars have argued that her critique of gender essentialism would have been difficult to formulate without Beauvoir's earlier rejection of biological determinism (Moi, 1999, p.90). Accordingly, Butler should be understood less as a rejection of Beauvoir than as an extension of Beauvoir's anti-essentialist project. Another significant development stresses on the relationship between recognition and structural inequality. Beauvoir mainly worked on domination through the existential relationship between subject and Other, emphasizing how patriarchal societies decline women equal recognition as autonomous subjects (Beauvoir, 2011, p.5). In this respect, Axel Honneth deepened this thought by saying that struggles for recognition constitute a fundamental dimension of social justice, linking individual identity formation to broader institutional patterns of respect, rights, and solidarity (Honneth, 1995, p. 95). Similarly, Nancy Fraser states that gender justice requires both cultural recognition and material redistribution, illustrating that symbolic exclusion and economic inequality are mutually reinforcing rather than analytically separable (Fraser, 2022, p.3). Together, these perspectives broaden Beauvoir's existential analysis by situating struggles for freedom within institutional, economic, and political structures. Accordingly, recent scholars increasingly examines Beauvoir's concepts of otherness, freedom, and transcendence to emerging issues such as digital surveillance, algorithmic discrimination, online gender-based violence, and platform governance (Noble, 2018, pp.1–2). Nevertheless, these studies often address these developments separately, while relatively few provide a holistic framework connecting Beauvoir's existential feminism with contemporary debates on digital patriarchy, intersectionality, and algorithmic governance. Addressing this theoretical gap constitutes one of the principal objectives of the present study.

To illustrate the theoretical basis better it is crucial to do an analysis of Kimberlé Crenshaw's theory of intersectionality. It represents another major expansion of feminism. Beauvoir's analysis primarily examined women's subordination through the universal category of gender, paying comparatively limited attention to how race, ethnicity, class, disability, sexuality, and colonial histories shape different experiences of oppression. Crenshaw (1989, p.140) challenged universalizing approaches by demonstrating that gender discrimination cannot be

fully understood independently of other systems of power that created unfair practices. Black women, for example, experience forms of discrimination that cannot be explained solely through gender or race in isolation but emerge from their simultaneous interaction. Intersectionality therefore is a complementary aspect to Beauvoir's concept of otherness by unveiling that processes of exclusion are multidimensional and historically situated rather than uniform across all women.

Iris Marion Young further contributes to this discussion by shifting attention from individual experiences of discrimination toward structural forms of oppression embedded within social institutions. Young (1990, p. 36) states that injustice is created through institutional processes that normalize exploitation, marginalization, powerlessness, cultural domination, and violence. This structural perspective reinforces Beauvoir's claim that women's inequality cannot be reduced to individual prejudice or personal attitudes but instead reflects deeply embedded institutional arrangements. However, Young extends Beauvoir by providing a more systematic account of how political, legal, and economic institutions reproduce unequal power relations across society.

Recent feminist scholarship has also expanded these debates into the realm of technology and digital governance. Scholars such as Safiya Umoja Noble (2018, p.2) states that algorithmic systems continuously constructs gendered and racialized inequalities through search engines and digital infrastructures. Likewise, D'Ignazio and Klein (2020, p.8) states that data practices are never politically neutral but instead reflect the social values embedded within technological systems. These contributions suggest that contemporary patriarchal domination forms increasingly operate through algorithmic decision-making, platform governance, and AI rather than only through traditional legal or cultural institutions. Consequently, feminist theory has gradually expanded from analyzing institutional patriarchy toward examining the governance of gender within digital societies.

Despite these significant theoretical developments, an important gap remains within the literature. Existing studies generally pursue one of two directions. The first examines Beauvoir as a foundational philosopher of existential feminism, while the second analyses contemporary issues such as algorithmic bias, digital violence, and platform governance through more recent feminist frameworks (Noble, 2018, p.2). Comparatively few studies have systematically integrated Beauvoir's existential concepts with contemporary analyses of digital patriarchy within a single analytical framework. This fragmentation limits our ability to understand the continuity between classical and technologically mediated forms of gender inequality. Addressing this limitation constitutes one of the principal objectives of the present study and provides the rationale for developing the Contemporary Otherness Framework presented in the following sections.

While Beauvoir's existential feminism remains one of the most significant definitions of women's oppression, modern gender politics has been transformed by globalization (Fraser, 2022, p.7), digitalization, AI, algorithmic governance, and platform capitalism (Noble, 2018, p.2). Although these developments have generated feminist scholarship, the literature remains fragmented. Studies inspired by Beauvoir mainly sheds light on philosophical understanding, whereas research on digital patriarchy and algorithmic discrimination often develops

independently of existential feminist theory. Consequently, existing scholarship offers limited integration between classical feminist concepts and contemporary forms of gendered power.

To address this gap, this article proposes the Contemporary Otherness Framework (COF) as an integrative analytical model that extends Beauvoir's existential feminism by incorporating contemporary debates on digital governance, intersectionality, recognition, and structural power. The framework conceptualizes gender inequality as a dynamic process in which patriarchal institutions adapt to changing political, technological, and social conditions while preserving the fundamental logic of othering.

The COF comprises five interconnected dimensions:

**(1) otherness**, refers to the institutional construction of women as subordinate subjects; (Beauvoir, 2011, p. 6; Honneth, 1995, p.95)

**(2) freedom**, examines how structural inequalities restrict women's existential and political agency; (Young, 1990, p.33)

**(3) immanence and transcendence**, analyses how patriarchal institutions limit opportunities for self-realization while women continue to challenge these limitations; (Beauvoir, 2011, p.726)

**(4) anti-essentialism**, understands gender as socially and institutionally constructed rather than biologically predetermined (Butler, 1990, p.25) and

**(5) adaptive patriarchy**, explains how modern technologies—such as AI, algorithmic governance, digital surveillance, and platform economies—creates historical patterns of gender domination through new institutions (Noble, 2018, p.2).

**Table 1:** The Definition of COF Components

| COF Component     | Operational Definition                                       | Empirical Indicator                                                                     |
|-------------------|--------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| Otherness         | Institutional construction of women as secondary subjects    | Legal restrictions, discriminatory discourse, algorithmic bias                          |
| Freedom           | Capacity for autonomous agency and decision-making           | Access to education, work, political participation, bodily autonomy                     |
| Immanence         | Institutional confinement to repetitive or subordinate roles | Domestic confinement, exclusion from employment, platform-driven aesthetic labour       |
| Transcendence     | Individual or collective practices challenging domination    | Protest movements, digital activism, underground education, feminist mobilization       |
| Anti-essentialism | Rejection of biologically predetermined gender roles         | Legal reforms, inclusive policies, counter-narratives, resistance to gender stereotypes |

*Source: Prepared by the author.*

Unlike existing feminist frameworks, the COF does not treat existential philosophy, recognition theory, intersectionality, and digital governance as separate analytical perspectives. Instead, it conceptualizes them as mutually reinforcing dimensions of a single adaptive process through which patriarchal domination is continuously reproduced under changing institutional conditions. Consequently, the COF offers an original theoretical contribution by bridging classical existential feminism with contemporary debates on digital societies within a unified explanatory framework. Rather than functioning solely as a reinterpretation of Beauvoir's philosophy, the framework provides a transferable analytical model that can be applied comparatively across diverse political, legal, cultural, and technological contexts to explain both the continuity and the transformation of gender inequality in the twenty-first century.

The distinctive contribution of the COF lies not only in integrating Beauvoir's existential concepts with contemporary feminist debates but also in differentiating how patriarchal domination operates across diverse institutional settings. Rather than assuming that the same mechanisms of inequality function uniformly across all cases, the framework identifies the dominant configuration of its five analytical dimensions within each context. In Iran, institutional otherness is primarily reproduced through state regulation, compulsory veiling, and legal restrictions, while women's resistance illustrates the tension between immanence and transcendence. In Afghanistan, the dominant mechanism is the systematic restriction of existential freedom through the exclusion of women from education, employment, and public life under Taliban rule. By contrast, digital societies are characterized less by direct legal coercion than by adaptive patriarchy, in which algorithmic governance, platform capitalism, and artificial intelligence mediate recognition and reproduce gender inequality through computational systems (Noble, 2018, p. 13; D'Ignazio & Klein, 2020, p. 8). Accordingly, the COF does not assume that all five dimensions are equally salient in every case; rather, it enables comparative analysis by identifying which dimensions become institutionally dominant under different political, cultural, and technological conditions.

At the same time, the explanatory scope of the COF is intentionally limited. The framework is designed to analyse institutionalized forms of gender inequality in which relations of domination are socially organized through political, legal, economic, or technological structures. It is not intended to explain all dimensions of gendered experience, nor does it replace context-specific analyses of culture, religion, ethnicity, or local historical conditions. Instead, these factors are treated as contextual variables that shape how the five dimensions of the COF are expressed in particular cases. Consequently, the framework should be understood as a comparative interpretive model whose analytical value lies in explaining variation in the institutional reproduction of gender inequality rather than proposing a universally deterministic theory of patriarchy.

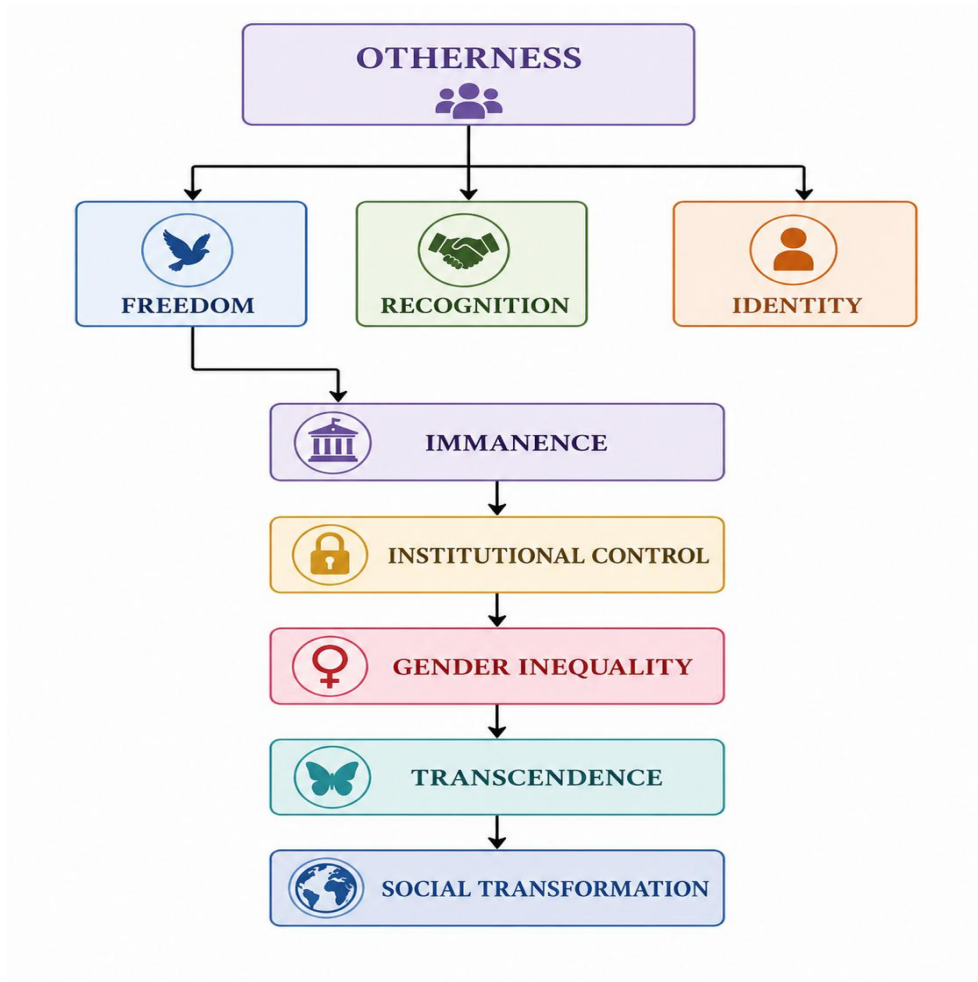


**Figure 1:** Components of Contemporary Otherness Framework

*Source: Prepared by the author.*

**Table 2:** Comparative Analytical Contribution of the Contemporary Otherness Framework (COF)

| Case                | Dominant Analytical Dimension(s)                                | Form of Patriarchal Domination                                            | COF Contribution                                                                                                                                           |
|---------------------|-----------------------------------------------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Iran                | Otherness; Immanence–Transcendence                              | Legal and state-centred domination                                        | Explains how institutional otherness generates collective resistance and the pursuit of transcendence.                                                     |
| Afghanistan         | Freedom; Immanence                                              | Systematic exclusion through political and religious institutions         | Demonstrates how the denial of existential freedom becomes the dominant mechanism of patriarchal control.                                                  |
| Digital Governance  | Adaptive Patriarchy; Otherness                                  | Algorithmic governance and AI                                             | Shows how historical patterns of domination are reproduced through computational infrastructures rather than direct legal coercion.                        |
| Platform Capitalism | Adaptive Patriarchy; Anti-essentialism; Immanence–Transcendence | Platform economies, digital beauty culture, and commercialized visibility | Illustrates how patriarchal power adapts to digital capitalism by transforming identity, visibility, and self-presentation into market-oriented practices. |

*Source: Prepared by the author.*

## 4. Case Studies and Analysis

### *4.1. Mahsa Amini and the Politics of Otherness: State Control, Bodily Autonomy, and Existential Freedom*

Mahsa Amini's death in custody in September 2022 represents one of the most clear modern examples of how patriarchy repeatedly regulate women's bodies through legal, political, and ideological institutions. Arrested by Iran's Guidance Patrol for allegedly violating compulsory hijab regulations, Amini died while in police custody, under surveillance, triggering nationwide protests that rapidly evolved into the largest challenge to the Islamic Republic in decades. The demonstrations, organized under the slogan "*Woman, Life, Freedom*" (*Zan, Zendegi, Azadi*), extended far beyond opposition to compulsory veiling and developed into a broader movement asking for bodily autonomy, political participation, and fundamental human rights (Amnesty International, 2024).

From the lens of Beauvoir's existential feminism, the case of Mahsa Amini demonstrates the institutional construction of otherness. Beauvoir states that patriarchal societies maintain political authority by defining women not as autonomous subjects but as objects whose identities are determined through external norms and institutional control (Beauvoir, 2011, p.5). In Iran, compulsory dress regulations function not only as religious obligations but also as mechanisms through which the state shapes legitimate femininity and disciplines women's presence within public realm. Consequently, women become subjects of regulation rather than agents capable of determining their own bodily identities.

This institutional creation of otherness restricts existential freedom. Beauvoir further argues that freedom demands individuals to participate freely in determining the conditions of their own existence rather than merely complying with externally imposed identities (Beauvoir, 1948/1976, p.10). The compulsory regulation of women's appearance therefore represents more than a limitation on personal choice; it constitutes a rejection of existential agency. Women's bodies become political objects through which state authority is continuously reconstructed, decreasing opportunities for autonomous self-definition and reinforcing domination relations.

While Beauvoir's concept of otherness provides a valuable analytical lens for interpreting the institutional subordination of women in Iran, this case also illustrates the limitations of applying a framework developed within the intellectual traditions of twentieth-century European existentialism to a non-Western context. The Kurdish experience is shaped not only by gender but also by the interaction of religion, state authority, national politics, and ethnic identity, particularly in the case of Mahsa Amini as a Kurdish woman. As postcolonial feminist scholars argue, universal applications of Western feminist theories risk overlooking the historical and cultural specificities of non-Western societies (Mohanty, 1988, pp. 61–63; Abu-Lughod, 2002, pp. 784–785). Accordingly, Beauvoir's framework should not be understood as a universally exhaustive explanation but rather as an interpretive perspective that gains analytical depth when combined with intersectionality and context-sensitive feminist approaches (Crenshaw, 1989, p. 140). As a woman subjected to state regulation, her oppression emerged through the interaction of gender, ethnicity, religion, and authoritarian governance, illustrating Crenshaw's argument that systems of domination operate simultaneously rather than independently (Crenshaw, 1989, p. 140).

The case likewise illustrates the analytical value of the COF proposed in this study. The Iranian state institutionalizes otherness through legal regulation, restricts existential freedom by limiting bodily autonomy, reinforces immanence through compulsory gender norms, and justifies these practices through essentialist understandings of femininity, which eventually creates a false consciousness for consent-building. However, at the same time, public resistance shows that processes of othering continue to be historically contingent instead of being immutable. In this respect, the *"Woman, Life, Freedom"* movement represents not only political opposition but also an existential struggle for recognition, subjectivity, and equal participation in public realm. Therefore The case of Mahsa Amini is a concrete example of Beauvoir's theoretical insights that remain highly relevant for explaining how patriarchal domination continues to evolve under modern political conditions while simultaneously illustrating the explanatory capacity of the COF.

#### ***4.2. Taliban's Afghanistan: Institutionalized Immanence and the Denial of Existential Freedom***

Following the Taliban's return to power in August 2021, Afghanistan has experienced one of the most extensive reversals of women's rights in the 21st century. Through successive decrees, the Taliban prohibited girls from attending secondary schools and colleges, restricted women's employment in governmental and non-governmental organizations, imposed restrictions on freedom of movement, and progressively excluded women from the public realm. International organizations have characterized these measures as systematic forms of gender-based discrimination and oppression that affect almost every dimension of women's social, economic, and political participation (UN Women, 2023, p.4). Unlike temporary restrictions, these measures constitute a comprehensive institutional framework designed to redefine women's social existence. Education, employment, political participation, mobility, and public visibility have increasingly become conditional upon gender, creating a social order in which women are expected to remain primarily within domestic and family spheres which leads to long term segregation. Consequently, gender inequality is reproduced not only through individual acts of discrimination but through an interconnected system of legal, political, religious, and administrative institutions.

In this respect, the field of education occupies a crucial place within this framework. Beauvoir argues that freedom demands the capacity to pursue self-determined projects and continuously transcend existing circumstances (Beauvoir, 1948/1976, p. 25). Denying girls access to secondary and higher education therefore constitutes more than an educational policy; it represents a structural limitation on the development of agency, critical reasoning, and future life opportunities. Restricting education simultaneously narrows access to employment, political participation, and economic independence, reinforcing cycles of institutional dependency across generations.

The segregation of women from employment further supports Beauvoir's distinction between immanence and transcendence. Participation in economic life enables individuals to exercise autonomy, gain public recognition, and engage in collective decision-making. However, in contrast, the systematic exclusion of women from professional occupations corners them to socially reproductive labour while decreasing opportunities for independent social existence. Beauvoir stresses that oppression becomes institutionalized when individuals are prevented

from choosing among multiple choices that shape life and are instead assigned predetermined identities in accordance with socially constructed gender roles (Beauvoir, 2011, p.489). The exclusion of Afghan women from education, employment, and public life similarly reflects intersecting structures of gender, political authoritarianism, religion, and economic dependency. Consequently, the Taliban's policies demonstrate multiple and mutually reinforcing forms of inequality rather than a single axis of gender discrimination (Crenshaw, 1989, p. 140).

The Case of Afghanistan also illustrates how the continuing relevance of Beauvoir's concept of otherness is relevant. Taliban regulations construct women not as equal political subjects but as individuals whose public presence requires continuous supervision and restriction which puts women under surveillance. Women's participation in education, employment, and public sphere is regulated through externally imposed norms rather than individual autonomy. As Beauvoir argues, patriarchal systems maintain domination by defining women through dependence and difference rather than equal subjectivity (Beauvoir, 2011, p.5). In the case of Afghanistan, this process becomes institutionalized through formal legal and administrative mechanisms, illustrating how otherness operates as a principle of governance rather than merely a cultural attitude.

Modern feminist scholars further stresses on this interpretation. For example Nancy Fraser states that gender injustice cannot be evaluated separately from a wider perspective of institutional arrangements that organize social reproduction and political participation (Fraser, 2022, p.3). Likewise, Iris Marion Young conceptualized oppression as a structural phenomenon reproduced through institutional processes rather than isolated acts of discrimination (Young, 1990, p.36). These perspectives complement Beauvoir's existential analysis by illustrating that women's exclusion from public life reflects systemic patterns of domination embedded within political institutions rather than individual prejudice alone.

However, although Beauvoir's concepts of freedom, immanence, and otherness illuminate the structural exclusion of women from education, employment, and public life, the Taliban's gender regime cannot be fully understood through existential feminism alone. The political significance of religion, tribal traditions, prolonged armed conflict, and state fragility creates a context that differs substantially from the historical conditions under which Beauvoir developed her theory. Consequently, this study interprets Beauvoir's concepts as analytical rather than universal categories and complements them with intersectional and institutional perspectives that recognize the contextual diversity of gender oppression (Mohanty, 1988, pp. 61–63; Fraser, 2022, p. 11).

The COF developed in this article provides an integrated understanding of these dynamics. Within the Afghan context, patriarchal institutions construct women as the "Other," restrict existential freedom through legal prohibitions, reinforce immanence by excluding women from education and employment, and legitimize these restrictions through essentialist interpretations of gender roles. The interaction of these mechanisms produces a self-reinforcing system in which legal regulation, institutional authority, and cultural norms collectively reproduce women's exclusion from public sphere.

At the same time, Afghan women's repeated initiatives to access education, establish underground schools, engage in digital activism, and document human rights violations

demonstrate that existential freedom cannot be completely extinguished by institutional domination. These forms of resistance demonstrate Beauvoir's assumption that human beings remain capable of projecting themselves beyond oppressive conditions, even when opportunities for transcendence are severely constrained (Beauvoir, 1948/1976, p.72). Accordingly, the Afghan case confirms both the continuing explanatory power of Beauvoir's existential feminism and the analytical utility of the COF for understanding contemporary forms of institutionalized gender oppression.

#### ***4.3. Digital Patriarchy, Artificial Intelligence, and Algorithmic Governance***

The rapid expansion of artificial intelligence (AI), machine learning, algorithmic governance, and data-driven decision-making has fundamentally transformed the institutional mechanisms through which gender inequality is produced and reproduced. Contemporary digital technologies increasingly influence access to information, employment, finance, healthcare, security, and political participation by relying on automated systems that classify, rank, and evaluate individuals according to computational criteria. Although these technologies are frequently presented as objective and politically neutral, growing evidence demonstrates that algorithmic systems often reproduce existing social inequalities because they are trained on historical datasets and embedded within unequal institutional structures (O'Neil, 2016, p.3). Rather than replacing traditional patriarchal institutions, digital technologies have enabled patriarchal power to operate through increasingly sophisticated computational mechanisms.

From the perspective of Simone de Beauvoir's existential feminism, these developments should not be interpreted as entirely new forms of domination but rather as contemporary transformations of otherness. In *The Second Sex*, Beauvoir argues that patriarchal societies deny women full subjectivity by constructing them as the "Other," whose identity is determined through external definitions rather than autonomous self-determination (Beauvoir, 2011, p.5). Algorithmic governance reproduces a similar logic by reducing individuals to data profiles, behavioural predictions, and automated classifications that influence opportunities for participation, visibility, and social recognition. Consequently, women increasingly become subjects of computational evaluation rather than autonomous agents exercising control over the conditions of their own existence.

One of the clearest manifestations of this transformation is the emergence of deepfake technologies and AI-generated synthetic media. Advances in generative AI enable the creation of highly realistic fabricated images and videos without the knowledge or consent of the individuals represented. Publicly documented cases demonstrate that the overwhelming majority of victims of deepfake pornography are women, whose digital identities become objects of technological manipulation, commodification, and sexual exploitation (Chowdhury & Lakshmi, 2023). This causes women's bodies to not function as expressions of autonomous subjectivity and instead become digitally reproducible objects detached from individual agency. In this sense, AI does not merely facilitate new technological harms but reproduces the same logic of unequal subjectivity.

Algorithmic bias constitutes another important mechanism through which digital patriarchy becomes institutionalized. Machine learning systems frequently rely on historical datasets that reflect existing inequalities, allowing discriminatory assumptions to become embedded within

automated decision-making processes. Research has demonstrated that algorithmic systems may reproduce gender bias in employment recruitment, credit assessment, predictive policing, image recognition, healthcare, and online content moderation (O'Neil, 2016, p. 3; Noble, 2018, p. 13). Rather than eliminating human prejudice, computational systems frequently inherit and amplify structural inequalities already present within society. Consequently, algorithmic governance should be understood not as a neutral technological innovation but as an institutional mechanism capable of reproducing historically embedded relations of domination through automated processes (D'Ignazio & Klein, 2020, p.8).

These developments also have important implications for Beauvoir's understanding of existential freedom. Beauvoir argues that freedom requires individuals to participate actively in shaping the conditions of their own existence rather than merely adapting to externally imposed identities (Beauvoir, 1948/1976, p. 19). However, algorithmic governance increasingly influences access to employment opportunities, financial services, public information, and digital participation through opaque computational systems that remain largely inaccessible to those affected by their decisions. As a result, women's opportunities for autonomous agency become constrained not only by legal or political institutions but also by technological infrastructures operating through invisible forms of surveillance, prediction, and automated evaluation (D'Ignazio & Klein, 2020, p.8).

The relevance of intersectionality further strengthens this analysis. Crenshaw (1989, p.140) argues that systems of domination rarely operate through a single axis of inequality but instead emerge through the interaction of gender, race, ethnicity, class, and other forms of social differentiation. Digital technologies reproduce similar dynamics. Algorithmic systems frequently generate disproportionate disadvantages for women belonging to racial, ethnic, religious, or economically marginalized communities because historical patterns of discrimination become encoded within computational models. Accordingly, digital patriarchy should be understood not only as gendered domination but also as an intersectional process in which multiple forms of inequality become institutionalized through technological infrastructures.

Viewed through the Contemporary Otherness Framework (COF), these developments demonstrate that patriarchal domination has undergone institutional transformation rather than historical disappearance. Within digital societies, otherness is reproduced through algorithmic classification, existential freedom is constrained by opaque systems of automated governance, and unequal recognition is increasingly mediated through computational decision-making rather than solely through traditional legal or religious institutions. The mechanisms of domination have changed substantially, yet the underlying logic identified by Beauvoir—the denial of women as fully autonomous subjects—remains analytically intact. The COF therefore extends Beauvoir's existential feminism beyond its original historical context by demonstrating how contemporary digital governance reproduces classical structures of patriarchal power through technologically mediated institutional arrangements.

**Table 3:** Classical and Contemporary Patriarchy Comparison

| Classical Patriarchy  | Contemporary Patriarchy     |
|-----------------------|-----------------------------|
| State                 | State + Algorithms          |
| Religion              | Platforms                   |
| Family                | AI                          |
| Labour Division       | Platform Economy            |
| Domestic Space        | Digital Space               |
| Physical Surveillance | Digital Surveillance        |
| Bodily Control        | Data Control                |
| Objectification       | Algorithmic Objectification |

*Source: Prepared by the author.*

#### **4.4. Platform Economies, Digital Beauty Culture, and the Reconstruction of Immanence**

While algorithmic governance institutionalizes gender inequality through automated decision-making, digital platforms transform patriarchal power through the commercialization of visibility, identity, and self-presentation. Social media platforms such as Instagram, TikTok, and YouTube have become central arenas in which femininity is produced, evaluated, and commodified through platform-specific economic logics. Rather than functioning merely as communication technologies, these platforms constitute economic ecosystems that convert visibility into symbolic and financial capital by rewarding continuous user engagement, aesthetic conformity, and audience attention (Abidin, 2016, p.90; Duffy & Hund, 2015, p.3). Consequently, women's digital participation increasingly occurs within commercial environments where personal identity itself becomes a marketable asset.

The platform economy further intensifies these dynamics by transforming personal visibility into economic value. Influencer marketing, sponsored content, affiliate advertising, and creator monetization systems enable individuals to generate income through digital self-presentation, thereby blurring the boundaries between personal identity and commercial performance (Abidin, 2016, p. 91). While these developments have undoubtedly created new opportunities for women to participate in digital economies, they also establish institutional incentives for continuous self-optimization and commercial self-branding. Success increasingly depends not only on professional competence but also on maintaining algorithmically desirable forms of femininity capable of attracting sustained audience engagement (Duffy & Hund, 2015, p.5).

Digital beauty culture further illustrates Beauvoir's critique of essentialist understandings of femininity. Photography filters, facial enhancement applications, and AI-assisted image-editing technologies continuously normalize particular facial proportions, body shapes, skin textures, and visual styles through repeated exposure and platform circulation. Rather than simply reflecting pre-existing beauty ideals, these technologies actively participate in producing and reinforcing socially constructed standards of femininity (Elias et al., 2017, p.26). This process directly supports Beauvoir's anti-essentialist argument that femininity is not biologically predetermined but socially produced through institutional and cultural practices.

Contemporary feminist scholarship conceptualizes these developments as manifestations of digital patriarchy, emphasizing that technological innovation does not automatically eliminate

gender inequality but frequently reorganizes existing relations of domination within new institutional settings (Banet-Weiser, 2018, p.147-152). Digital infrastructures increasingly influence whose bodies receive visibility, whose identities become commercially valuable, and whose experiences remain marginalized. Accordingly, platform governance should be understood not merely as an economic model but as a cultural institution that shapes social recognition by defining the norms through which femininity becomes visible, desirable, and economically profitable (Bucher, 2018, p.85; Gillespie, 2014, p.173).

These developments also reveal that recognition within platform societies has become increasingly dependent upon measurable indicators of popularity, including follower counts, engagement metrics, shares, comments, and audience interaction. Rather than achieving recognition solely through autonomous political agency or social participation, individuals increasingly negotiate recognition through platform metrics that reward continuous visibility and emotional labour (Honneth, 1995, p.95). As a consequence, women's identities become embedded within systems that simultaneously promise empowerment while reinforcing market-oriented forms of self-discipline and commercialized femininity.

Viewed through the Contemporary Otherness Framework (COF), platform economies demonstrate that patriarchal domination has adapted to contemporary digital capitalism by reconstructing rather than eliminating the historical distinction between immanence and transcendence. Women's opportunities for agency have undoubtedly expanded through digital participation; however, these opportunities remain conditioned by institutional expectations that reward continuous aesthetic performance, emotional availability, and commercial visibility. Consequently, platform capitalism does not simply reproduce historical forms of patriarchy but transforms them into economically mediated systems of gendered recognition. The COF therefore illustrates that contemporary patriarchal power increasingly operates through the interaction of market logics, digital infrastructures, and socially constructed ideals of femininity, extending Beauvoir's existential analysis into the political economy of platform societies.

## 5. Conclusion

This article examines the extent to which Simone de Beauvoir's existential feminist thought remains relevant for interpreting contemporary forms of gender inequality and explores how her key philosophical concepts can be adapted to contemporary debates on digital patriarchy and gender politics. While *The Second Sex* was written within the political and social context of the mid-twentieth century, the evidence shows that Beauvoir's central philosophical concepts continue to provide a powerful analytical framework for explaining how patriarchal power is reproduced under changing historical conditions. Rather than becoming theoretically obsolete, Beauvoir's concepts of otherness, freedom, immanence, transcendence, and anti-essentialism remain remarkably applicable to contemporary political, legal, and technological environments (Moi, 1999, p.63).

The first research question asked whether Beauvoir's existential feminism remains relevant for analysing twenty-first-century gender politics. The comparative analysis clearly suggests that the answer is affirmative. Across the four case studies examined, patriarchal domination continues to operate by limiting women's autonomy, regulating bodily agency, restricting

access to public participation, and reproducing unequal systems of recognition. Although the institutional mechanisms differ significantly between authoritarian political regimes and digitally mediated societies, the fundamental process identified by Beauvoir—the construction of women as the "Other"—remains a central mechanism through which gender inequality is reproduced (Beauvoir, 2011, p.5).

The second research question examined how Beauvoir's framework can be adapted to explain contemporary forms of gender inequality emerging within digital societies. The evidences indicate that technological innovation has not fundamentally transformed the logic of patriarchal domination; rather, it has altered its institutional expression. AI, algorithmic governance, platform economies, and social media infrastructures increasingly participate in shaping visibility, identity, and recognition. These technologies expand opportunities for participation while generating new forms of surveillance, commodification, algorithmic discrimination, and image-based gendered violence. Consequently, digital environments should not be interpreted as politically neutral realms but as institutional settings in which historical patterns of inequality acquire technologically mediated forms (D'Ignazio & Klein, 2020, p.8).

To address these developments, this study proposed COF as its main theoretical contribution. Unlike existing approaches that examine Beauvoir's concepts independently, the COF integrates otherness, freedom, immanence, transcendence, and anti-essentialism into a unified analytical model capable of explaining both classical and contemporary aspects of patriarchy. The framework argues that gender inequality emerges through the interaction of institutionalized otherness, constrained existential freedom, socially organized immanence, historically constructed gender identities, and the adaptive transformation of patriarchy. By combining these dimensions within an explanatory structure, the COF extends Beauvoir's existential feminism beyond its original historical context while preserving its central philosophical insights.

The comparative case studies further elaborates that patriarchal domination should not be conceptualized as a static or culturally specific phenomenon. Instead, it represents a dynamic process capable of adapting to different political systems, legal arrangements, and technological infrastructures. In Iran and Afghanistan, domination is mainly conducted through regulation, religious authority, and direct restrictions on women's education, mobility, and bodily autonomy. In digital environments, however, domination increasingly operates through algorithmic recommendation systems, AI, platform capitalism, and computational governance. Despite these institutional differences, both contexts reproduce unequal relations of recognition that restrict women's opportunities for autonomous subjectivity and existential freedom (Honneth, 1995, p.95).

It also contributes to broader feminist theory by illustrating that Beauvoir's existential philosophy remains compatible with important contemporary perspectives. Rather than competing with Butler's theory of performativity (Butler, 1990, p.25) Crenshaw's theory of intersectionality (Crenshaw, 1989, p.140), or Fraser's theory of redistribution and recognition (Fraser, 2022, p.11), Beauvoir's existential feminism provides a philosophical foundation upon which these later approaches can be situated. The present study therefore supports a complementary rather than competitive understanding of feminist theory, highlighting that

contemporary gender inequality studies require analytical frameworks capable of integrating existential, structural, institutional, and technological dimensions simultaneously.

Beyond its theoretical contributions, this research also carries practical implications. Policymakers, international organizations, and technology companies continuously face with challenges associated with gender-based segregation, online violence, algorithmic bias, and unequal digital participation. The evidence suggest that effective policy responses should extend beyond legal equality by addressing the institutional and technological mechanisms through which unequal recognition continues to be reproduced. Regulatory frameworks governing AI, platform accountability, digital privacy, and online gender-based violence should therefore incorporate feminist perspectives that recognize the interaction between technological innovation and social power (D'Ignazio & Klein, 2020, p.8).

Several limitations should nevertheless be underlined. This article is mainly conceptual and interpretive in nature and therefore does not seek to establish causal relationships through quantitative analysis. Future research could empirically operationalize the COF by employing comparative fieldwork, interviews, survey research, computational social science methods, or cross-national datasets. Additional studies may also highlight how emerging technologies—including generative AI, immersive virtual environments, biometric surveillance, and automated governance systems—reshape gender relations in different regional and cultural contexts (Noble, 2018, p.13).

In conclusion, more than seventy-five years after the publication of *The Second Sex*, Simone de Beauvoir's existential feminism continues to offer one of the most comprehensive philosophical approaches for understanding the persistence and transformation of gender inequality. While the institutional settings of patriarchal domination have evolved, the existential struggle for recognition, autonomy, and freedom remains central to women's experiences across globe. By proposing the COF, this article illustrates that Beauvoir's philosophy should be understood not merely as a historical contribution to feminist thought but as a living theoretical tradition capable of explaining the complexities of gendered power in the twenty-first century (Moi, 1999, p.63).

## **Declarations**

### ***Ethics Statement***

This study did not involve human participants, human subjects, interviews, surveys, experiments, or the collection of personal or identifiable data. The research relied exclusively on publicly available primary and secondary sources, including academic literature, legal documents, institutional reports, and policy publications. Therefore, ethical approval from an institutional research ethics committee was not required. The study was conducted in accordance with applicable research and publication ethics standards.

### ***Conflict of Interest***

The author declares that there is no conflict of interest related to the research, authorship, or publication of this article.

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RESEARCH ARTICLE

**The Geometry of Headlines: Typography, Page Position, and Visual Rhetoric in Turkish Newspaper Front Pages after Galatasaray's 2000 UEFA Cup Victory**

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**ABSTRACT**

This article examines how nine Turkish newspapers visually framed Galatasaray's 2000 UEFA Cup victory across 12 front pages published on 18–19 May 2000. The sample includes Akşam, Cumhuriyet, Fanatik, Hürriyet, Milliyet, Radikal, Sabah, Star, and Yeni Şafak. Using qualitative comparative visual analysis, the study considers headline typography, page position, color, photographic hierarchy, masthead treatment, and relations between words and images. Although the pages draw on the same match result and a limited pool of trophy photographs, they organize the victory in markedly different ways. Popular and sports newspapers favor oversized sans-serif type, yellow-red saturation, exclamation marks, starbursts, and headlines placed over photographs. Cumhuriyet and Radikal preserve greater editorial distance through restrained or ambivalent layouts. Other pages connect the club's victory to national symbols, the European Union debate, Çanakkale memory, and the 19 May holiday. The three 19 May pages shift attention from the trophy to urban crowds and public celebration. The findings show that layout operates as an editorial argument and that these late-analog pages gave the event durable visual form. Their short slogans, score blocks, high-contrast color fields, and poster-like compositions also share formal features with later digital sports graphics.

**Keywords:** *Galatasaray; UEFA Cup; Turkish press; typography; visual rhetoric*

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## **1. Introduction**

On 17 May 2000, Galatasaray AŞ played Arsenal FC in the UEFA Cup final at Parken Stadium in Copenhagen. The match ended 0-0 after extra time, and Galatasaray won the penalty shootout 4-1 to become the first Turkish club to win a major European football trophy (Union of European Football Associations [UEFA], 2000). When Turkish newspapers went to press, the design task extended beyond recording the score. Editors had to decide how large the trophy image should appear, how words and photographs should meet, which colors and symbols should frame the result, and what emotional register the page should adopt. Through those choices, a match result was given the visual language of national pride, popular spectacle, political metaphor, and commemorative display.

The timing added two layers of meaning. The victory came one day before 19 May, the Turkish public holiday officially marking the Commemoration of Atatürk, Youth and Sports Day. It also followed the Helsinki European Council's recognition of Turkey as a candidate for European Union membership by only a few months (European Council, 1999). The "Copenhagen criteria" were already familiar from the political and economic conditions of accession defined in 1993 (European Council, 1993). Copenhagen could therefore signify both the venue of the final and Turkey's contested relationship with Europe. Arsenal likewise offered a convenient shorthand for England and historical rivalry. These associations allowed the cup to carry meanings of recognition, belonging, and redress beyond the match itself.

This article examines how such associations are built through headline typography and page position. It considers scale, type style, color, overlap with photography, masthead relations, flags, starbursts, score boxes, side columns, aerial crowd photographs, and promotional labels. Treated as visual rhetorical acts, the pages give emotion spatial form and variously frame the victory as monumental, chaotic, sacred, ironic, disciplined, national, or commercial.

The corpus supports close comparison because the pages begin with much of the same raw material: a trophy-lifting photograph, the 4-1 penalty score, a claim of historical firstness, and Galatasaray's yellow-red palette. Their layouts nevertheless diverge. Some foreground disbelief, affection, or popular humor. Others adopt the tone of historical record, political commentary, or national ceremony. The three available 19 May pages move toward crowd photographs, urban space, and the public holiday. These differences make it possible to study layout as a visible form of editorial argument.

After establishing the theoretical framework and explaining the corpus, the article examines oversized display type, political and ideological metaphors, contrasting forms of editorial authority, and the limited 19 May aftermath subset. It then considers color, mastheads, newspaper identity, and the relationship between these printed pages and later digital sports graphics.

## **2. Literature Review and Theoretical Framework**

### ***2.1. Visual Semiotics and the Newspaper Page***

Visual semiotics provides the main analytical foundation. Barthes's theory of myth treats mass-cultural signs as second-order systems in which an already meaningful sign becomes the form of a broader ideological message (Barthes, 1972). A trophy-lifting photograph denotes a

football team holding a cup, yet the same image can connote recognition in Europe, national confirmation, historical correction, or collective destiny. Barthes's account of image-text relations is equally important because headlines anchor possible photographic meanings (Barthes, 1977). In this corpus, "Allah'ım! İnanamıyorum" ["My God! I can't believe it"] anchors the image in shock and awe, "Söke söke kupa" ["We wrested the cup away"] stresses hard-won conquest, and "Kupa G. Saray'ın" ["The cup is Galatasaray's"] adopts the tone of documentary record.

Kress and van Leeuwen's social-semiotic grammar supplies the compositional vocabulary for this reading, especially information value, salience, framing, and modality (Kress & van Leeuwen, 2006). A headline's position, its scale beside a photograph, and any overlap between word and image reveal the page's hierarchy. Van Leeuwen's account of color directs attention to color schemes and their cultural work rather than to isolated hues (van Leeuwen, 2011). Here, yellow and red operate as club colors, festive codes, high-visibility commercial devices, and signs of emotional warmth.

Visual rhetoric shifts the question from what a sign means to the function it performs within the composition. Foss (2005) proposes studying a visual artifact through its nature, function, and evaluation. Applied to a front page, this approach helps distinguish celebration, commemoration, political analogy, and souvenir-like presentation as formal possibilities. Rose's (2016) critical visual methodology also requires attention to the image, its production setting, and the site of audiencing. The present study examines the pages and visible traces of production logic. Research on visual framing treats media content and audience effects as distinct empirical problems. Geise and Xu's (2025) systematic review shows that sensory, affective, cognitive, and behavioral claims depend on dedicated effects research. Because this study has no reception evidence or newsroom interviews, references to address, alignment, or invitation describe features encoded in the design rather than measured audience effects.

## ***2.2. Typography, Layout, and Newspaper Form***

Typography is central because these headlines are read as language and seen as images. Lupton (2010) defines typography as the arrangement of letters, words, and paragraphs within visual systems. Display type therefore registers first as weight, width, contour, shadow, color, and spatial pressure. Harrower and Elman (2013) treat headlines, photographs, text blocks, logos, and white space as parts of page architecture. García's (1993) structural approach makes a related point: visual hierarchy emerges from the coordination of type, layout, and color. Across these pages, the event remains constant while the hierarchy that presents it changes.

Barnhurst and Nerone's (2001) history of newspaper form frames visible organization as a mode of cultural authority. A front page can address its public as citizens, consumers, fans, witnesses, mourners, or participants in celebration. These are implied positions in the design, not evidence of actual response. Cumhuriyet's restrained grid offers civic distance, Fanatik's saturated poster aligns with supporter immersion, Hürriyet's flag and Atatürk silhouette place the victory within a national frame, and Radikal's juxtaposition of celebration and disorder creates a more critical viewing position.

Recent research confirms the front page's role as an editorial form. Serafis and Tseronis (2023) show how headlines, images, and page organization combine into multimodal arguments. Coche and Bell's (2024) study of more than 900 U.S. newspaper front pages demonstrates that prominence and ownership shape the visibility of sporting victories. Haught and Morris (2025) place such choices within a longer history of front-page design and draw attention to the spread of templates and visual sameness. Together, these studies support close attention to scale, position, and page architecture.

### ***2.3. Sport, National Identity, and Turkish Media Culture***

Sport journalism is a powerful site of national identification. Anderson's (1995) concept of imagined communities explains how print culture can represent dispersed people as sharing the same time and public feeling. Billig's (1995) banal nationalism draws attention to routine flags, collective pronouns, and references to the nation. The signs in this corpus are unusually emphatic: flags and Atatürk imagery move into the foreground, and a club victory is repeatedly framed as a national achievement.

Football scholarship adds historical and political context. Crolley and Hand (2002) show how European football writing draws on national, regional, and group identities. Boyle and Haynes (2009) describe sport, media, and popular culture as mutually shaping fields, while Giulianotti (1999) treats football as a global social game whose meanings extend beyond the pitch. For Turkey, Irak (2013) examines the sociopolitical relations surrounding football in Turkey and England, and Talimciler (2010) situates sport within popular culture and social transmission. Together, these studies support the treatment of front pages as media artifacts in which identity, memory, and power are organized visually.

Recent football-media research sharpens the link between sport and national identity. Ziaee et al. (2021) show how coverage can mobilize historical and political references in constructions of national identity. Mauro's (2025) comparison of British and Italian newspapers likewise traces nationhood through headlines, images, page composition, and editorial orientation. Their national-team cases provide a useful comparison for a club victory repeatedly recast as a national achievement. They also support reading the Çanakkale analogy, Atatürk imagery, European Union vocabulary, and collective pronouns as choices embedded in page design.

The Turkish media context further clarifies the visual intensity of the sample. Gencel Bek's (2004) study of tabloidization in television news identifies personalization, spectacle, visual density, and infotainment in a commercial media environment. Although the medium differs, these pressures help explain front pages that enlarge emotional language and package the event as an affective object. Arslan's (2018) discussion of Gürbilek's *Vitrinde Yaşamak* connects post-1980 culture to display, advertising language, and public images. Bora (2018) shows how political keywords condense ideological histories, while Ritchin (2009) provides a basis for comparing late-analog newspaper imagery with later digital forms.

The article addresses a specific gap: the visual construction of Galatasaray's 2000 victory on printed front pages. Sport-media research often emphasizes discourse, broadcasting, political economy, or fandom. Here, headline typography and page position serve as primary evidence. The page is treated as a designed field where editorial identity, commercial urgency, national symbolism, and sporting emotion meet.

### 3. Data Set and Method

The corpus contains 12 front pages from nine Turkish newspapers: Akşam, Cumhuriyet, Fanatik, Hürriyet, Milliyet, Radikal, Sabah, Star, and Yeni Şafak. Nine pages were published on 18 May 2000, immediately after the final. Three additional pages, from Fanatik, Milliyet, and Sabah, were published on 19 May and form a small follow-up subset. The unit of analysis is the front-page headline in its layout, including page position, scale, typographic treatment, color, relation to the masthead, photographic placement, and surrounding graphic elements.

The selection followed a purposive, archive-led strategy and does not claim statistical representativeness. A page was included when the title was a nationally distributed Turkish daily in print in May 2000, the Galatasaray victory was prominent on the front page, the headline and relevant layout features remained legible, and the page added a distinct visual or editorial configuration to the comparison. The sample combines the sports-specialist Fanatik with eight general-interest dailies and seeks variation in design language, commercial orientation, and editorial positioning, factors that recent comparative studies identify as relevant to front-page prominence and national framing (Coche & Bell, 2024; Mauro, 2025). Local newspapers, later commemorative pages, duplicate editions, and scans too incomplete for page-level analysis were excluded. The result is a bounded case set that supports analytical comparison and does not serve as a circulation-weighted account of the entire Turkish press.

**Table 1.** Corpus Composition and Analytical Role

| Newspaper  | Date        | Main visible headline (English translation)                                                                        | Role in corpus                                 |
|------------|-------------|--------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| Akşam      | 18 May 2000 | Allah'ım! İnanamıyorum (My God! I can't believe it)                                                                | 18 May core; affective display type            |
| Cumhuriyet | 18 May 2000 | Kupa G. Saray'ın (The cup is Galatasaray's)                                                                        | 18 May core; restrained grid                   |
| Fanatık    | 18 May 2000 | Efsane Cimbom / UEFA Şampiyonu (Legendary Cimbom / UEFA Cup champions)                                             | 18 May core; sports-specialist poster          |
| Fanatık    | 19 May 2000 | Visible UEFA acrostic, provisionally Ulusun / Evlatları / Fatih'in / Aslanları (The nation's sons / Fatih's lions) | 19 May subset; cropped scan and crowd imagery  |
| Hürriyet   | 18 May 2000 | Yaşayın varolun (Long may you live)                                                                                | 18 May core; national-symbolic frame           |
| Milliyet   | 18 May 2000 | Cimbom tarih yazdı / Canım (Cimbom made history / My darling)                                                      | 18 May core; affectionate vertical display     |
| Milliyet   | 19 May 2000 | Sen ilahsın (You are a god)                                                                                        | 19 May subset; mythic and urban narrative      |
| Radikal    | 18 May 2000 | Söke söke kupa (We wrested the cup away)                                                                           | 18 May core; celebration beside civic disorder |
| Sabah      | 18 May 2000 | İşte tarih böyle yazılır (This is how history is written)                                                          | 18 May core; monumental inscription            |
| Sabah      | 19 May 2000 | Selam size kahramanlar (We salute you, heroes)                                                                     | 19 May subset; crowd and double-holiday frame  |
| Star       | 18 May 2000 | Cup'tık (We got the cup)                                                                                           | 18 May core; popular pun and historical memory |
| Yeni Şafak | 18 May 2000 | Muhteşem (Magnificent)                                                                                             | 18 May core; EU and Copenhagen metaphor        |

The study uses qualitative comparative visual analysis. Each page was read along eight axes: headline wording, approximate scale and position, typographic style and treatment, color scheme, the headline-photograph relation, masthead placement, symbolic references, and the implied reading path. This approach follows the multimodal premise that meaning is distributed across language, image, color, layout, and material display (Jewitt, 2014; Machin & Mayr, 2012). The coding is interpretive rather than quantitative. The comparison uses features that are visually verifiable, such as headline dominance, overlap with photography, masthead hierarchy, framed versus poster-like image treatment, and the density of secondary elements.

The two dates serve different analytical purposes. The nine 18 May pages record the immediate victory through the trophy, the score, the penalty shootout, and claims of historical firstness. The three 19 May pages shift toward crowds, city space, helicopters, open-top vehicles, goalkeeper narratives, and the national calendar. This second-day pattern applies only to Fanatik, Milliyet, and Sabah. It is treated as an illustrative sequence within the corpus and does not support a generalization about the Turkish press as a whole.

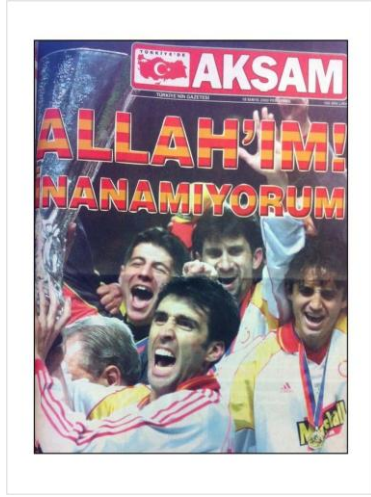
#### **4. Typography as a Shout: Scale and Visual Force**

On the 18 May pages, oversized display type often becomes the dominant image. Typography gives visual form to cheering, prayer, humor, commemoration, and chant. Read through Foss's (2005) account of rhetorical function and Lupton's (2010) treatment of type as a visual system, the letters matter for their verbal content and for the force they exert on the page.

Akşam places "ALLAH'IM! İNANAMIYORUM" ["MY GOD! I CAN'T BELIEVE IT"] across the top of its 18 May front page in enormous letters filled with yellow-red gradients (Akşam, 2000; Figure 1a). The apostrophe, exclamation mark, heavy outline, and color fill make disbelief visible as a public, devotional cry. Because the letters repeat Galatasaray's colors, the headline also works as a banner. "Allah'ım" carries an affective rather than doctrinal register, marking a moment when ordinary speech appears insufficient.

Sabah chooses a monumental register. "İŞTE TARİH BÖYLE YAZILIR" ["THIS IS HOW HISTORY IS WRITTEN"] dominates the page in massive black sans-serif type (Sabah, 2000a; Figure 1b). The scale presents the result as an inscription rather than a passing sports story. Black letterforms against a yellow field, with red accents, give the declaration visual weight while keeping it tied to Galatasaray's palette. The composition resembles a public tablet on which sporting history has already been recorded.

Milliyet develops a warmer version of monumental type (Milliyet, 2000a; Figure 1c). Near the masthead, "CİMBOM tarih yazdı" ["Cimbom made history"] introduces Cimbom, a popular nickname for Galatasaray. The word "CANIM" ["MY DARLING"] then runs vertically down the right side. The rotated trophy photograph leans into those black letters, giving affection a physical place in the composition. The orange-red frame, boxed secondary items, and the line "Türkiye sizinle gurur duyuyor" ["Turkey is proud of you"] combine the visual idioms of a poster, a love letter, and a national congratulation.



(a) Akşam, 18 May 2000



(b) Sabah, 18 May 2000



(c) Milliyet, 18 May 2000

**Figure 1.** Monumental and affective display strategies on 18 May 2000: (a) Akşam, (b) Sabah, and (c) Milliyet. Sources: Akşam (2000), Sabah (2000a), and Milliyet (2000a).

Star's headline reads "CUP'TIK" ["WE GOT THE CUP"], a visual pun on the Turkish word kaptık, meaning "we grabbed it" (Star, 2000; Figure 2a). By inserting the English word cup into a Turkish verb, the page domesticates a European institutional term and gives the victory a slangy, street-level voice. Its compact form and aggressive placement preserve the immediacy of a chant.

Hürriyet gives the shout an institutional frame. Its headline "YAŞAYIN VAROLUN" ["LONG MAY YOU LIVE"] is large and direct, yet much of its force comes from the surrounding Turkish flag, Atatürk silhouette, red masthead, and yellow-red border (Hürriyet, 2000; Figure 2b). The composition places a club victory inside an established national vocabulary and presents the newspaper as the public voice of congratulation.



(a) Star, 18 May 2000



(b) Hürriyet, 18 May 2000

**Figure 2.** Popular and national-institutional headline frames on 18 May 2000: (a) Star and (b) Hürriyet. Sources: Star (2000) and Hürriyet (2000).

Fanatik intensifies the visual language of the sports press (Fanatik, 2000a; Figure 3). "EFSANE CİMBOM" ["LEGENDARY CİMBOM"] appears in large yellow letters with red star motifs, while "UEFA ŞAMPİYONU" ["UEFA CUP CHAMPIONS"] stretches across the lower photographic field. The 4-1 score occupies a broad red block, and a starburst advertises "24 sayfa" ["24 pages"]. Score boxes, flags, borders, and the special-section promotion give the page the qualities of a supporter poster and a souvenir. Visual abundance takes priority over calm separation of elements.



(a) Fanatik, 18 May 2000

**Figure 3.** Fanatik's sports-poster composition on 18 May 2000. Source: Fanatik (2000a).

## 5. Graphic Construction of Political and Ideological Metaphors

Several pages incorporate political and ideological metaphors directly into their design. Comparable studies show how historical references and multimodal page choices can fold football into wider national narratives (Mauro, 2025; Ziaee et al., 2021). Starbursts, flags, masthead adjacencies, sidebars, and headline structures carry the argument. Bora's (2018) account of political keywords helps explain how a short phrase can activate a much longer ideological history when it is placed at the center of a front page.

Yeni Şafak uses the main headline "MUHTEŞEM" ["MAGNIFICENT"] and places beside it a starburst reading "KOPENHAG KRİTERLERİ: CİMBOM: 4 - ARSENAL: 1" ["COPENHAGEN CRITERIA: CİMBOM 4–1 ARSENAL"] (Yeni Şafak, 2000; Figure 4a). The joke joins the city of the final to one of the period's most recognizable terms in Turkey's European Union debate. The 1993 European Council defined the accession criteria, and the 1999 Council placed Turkey within the candidacy framework only months before the match (European Council, 1993, 1999). The starburst recasts the score as an answer to Europe in its own political vocabulary.

Star draws on a different historical script. A sidebar links Arsenal to Çanakkale by suggesting that the English, who could not pass the Turkish ancestors there, could not pass Galatasaray either (Star, 2000). Arsenal is thus framed as a sign of England, and the match is folded into a narrative of national resistance. Crolley and Hand (2002) show that football writing often relies on national stereotypes and inherited historical scripts. Star makes that process visible by placing the analogy beside its punning headline.

Hürriyet builds national legitimacy through a more official visual grammar (Hürriyet, 2000). The Turkish flag and Atatürk silhouette sit near the masthead, while yellow-red bands organize the page edges. Billig's (1995) account of national flagging explains the mechanism, although the signs here are enlarged rather than routine. Their placement frames Galatasaray's achievement as a success worthy of national recognition.

Within the three-page 19 May subset, Milliyet links football to the national calendar (Milliyet, 2000b; Figure 6a). The headline "SEN İLAHSIN" ["YOU ARE A GOD"] draws on Fatih Terim's reported words to Taffarel before the penalties. A nearby starburst reads "ATAM işte Gençlik ve Spor" ["ATATÜRK, THIS IS YOUTH AND SPORT"], using Atam as a patriotic form of address to Atatürk. The page places the goalkeeper's mythic elevation, the holiday, and the crowd inside one image field.

Sabah's 19 May page uses the smaller phrase "ÇİFTE bayram" ["A DOUBLE CELEBRATION"] near the masthead and the large central greeting "SELAM SİZE KAHRAMANLAR" ["WE SALUTE YOU, HEROES"] (Sabah, 2000b; Figure 6c). The coincidence of date, crowd photograph, and heroic salutation links the UEFA victory with the public holiday. The national framing emerges from their combination rather than from a single state emblem.

Radikal places the colloquial headline "SÖKE SÖKE KUPA" ["WE WRESTED THE CUP AWAY"] beside a photograph of street disorder and a caption critical of those who cast a shadow over the celebration (Radikal, 2000; Figure 4b). The juxtaposition acknowledges the victory while withholding a seamless image of public harmony. The available design evidence supports the narrower claim that celebration and civic anxiety occupy the same visual field. Its rhetoric is therefore ambivalent.



(a) Yeni Şafak, 18 May 2000

(b) Radikal, 18 May 2000

**Figure 4.** Political metaphor and editorial ambivalence on 18 May 2000: (a) Yeni Şafak and (b) Radikal.  
Sources: Yeni Şafak (2000) and Radikal (2000).

## 6. Rational Design and Emotional Density

The contrast between Cumhuriyet and the more explosive pages concerns performances of editorial authority, not a hierarchy of good and bad design. Cumhuriyet preserves the page as a controlled record. Star, Akşam, Fanatik, Sabah, Milliyet, and Yeni Şafak borrow the density and immediacy of a poster. Radikal combines a large colloquial headline with a split layout that interrupts pure celebration.

Cumhuriyet's 18 May front page is organized around a red masthead, a centered serif headline, explanatory text, and a rectangular trophy photograph inside a controlled grid (Cumhuriyet, 2000; Figure 5). "Kupa G. Saray'ın" ["The cup is Galatasaray's"] is prominent without overrunning the page. A line above it records the historical first, and a right-hand column reports celebrations in the streets. The photograph remains a bounded news image beneath the text rather than serving as a full-page background.



(a) Cumhuriyet, 18 May 2000

**Figure 5.** Cumhuriyet's restrained grid and bounded trophy photograph on 18 May 2000. Source: Cumhuriyet (2000).

This arrangement can be described as archival. It establishes distance while the event is still unfolding and translates celebration into a civic record. Barnhurst and Nerone (2001) help explain why the visible separation of evidence, caption, headline, and editorial judgment carries authority. The restrained color density matters as well. Yellow and red remain visible in the photograph and page accents without taking over the whole composition.

Radikal creates distance through juxtaposition rather than visual quiet (Radikal, 2000). "SÖKE SÖKE KUPA" is large, black, and colloquial, yet the central area is divided between celebration and disorder. The cup photograph encounters a counter-image, preventing the page from settling into uncomplicated triumph. Tabloid-scale typography and a critical editorial structure coexist in the same layout.

Milliyet combines emotion with a strong organizing logic across its two pages. On 18 May, "CANIM" forms a vertical axis against which the trophy image leans (Milliyet, 2000a). On 19 May, "SEN İLAHSIN" gives Taffarel a mythic role, while side columns, summary items, and player quotations reconstruct the penalty shootout through backstage voices (Milliyet, 2000b). An aerial crowd photograph supplies spectacle, but the surrounding text keeps the page legible as a multi-part report. Affection, quotation, urban celebration, and the national holiday are held within a dense but ordered design.

Front-page design also constructs an implied relation between newspaper and audience. Cumhuriyet adopts the voice of a restrained recorder. Radikal pairs celebration with critical distance, while Fanatik aligns its page with supporter immersion. Akşam and Star draw on popular idiom. Hürriyet institutionalizes the victory through national symbols, and Sabah alternates between monumental inscription and mass greeting. Yeni Şafak folds current political vocabulary into the celebration, while Milliyet combines affection, mythic quotation, and urban documentation. These positions describe cues in the layouts and should not be read as evidence of how audiences actually responded.

### **7. 19 May Subset: Crowd and Urban Space**

Three pages in the corpus date from 19 May, all from Sabah, Milliyet, and Fanatik. Within this limited subset, trophy imagery gives way to aerial crowds, public squares, open-top vehicles, helicopters, and goalkeeper narratives. The pattern indicates an aftermath shift from sporting achievement to urban celebration in these three titles. It does not support a general claim about the Turkish press as a whole.

Milliyet's 19 May page uses a large aerial photograph of a dense crowd around vehicles and a helicopter (Milliyet, 2000b; Figure 6a). Seen from above, individuals merge into a textured field of red, yellow, and dark movement. A smaller inset shows the team bus, flags, and supporters. The aerial viewpoint offers visual evidence of spatial scale that ordinary street-level sight could not provide. Within this page, the victory is represented as an event that occupies the city.

Fanatik's 19 May page supports a cautious reading of the same macro-spatial logic (Fanatik, 2000b; Figure 6b). The vertical acrostic can be read provisionally as "Ulusun / Evlatları / Fatih'in / Aslanları" ["The nation's / sons / Fatih's / lions"], with the initial letters spelling UEFA. The oversized letters organize helicopter and crowd images across the page, using the European institution's acronym as a structure for patriotic praise.

Sabah's 19 May page organizes several scales of heroization (Sabah, 2000b; Figure 6c). "SELAM SİZE KAHRAMANLAR" stretches across the center above a dense Taksim crowd. At the top, Taffarel is associated with the phrase "Golü kurtaran Tanrı'nın eliydi" ["It was God's hand that made the save"], while Fatih Terim appears with the cup at the right. The lower headline "Penaltılarda ağladık" ["We cried during the shootout"] returns the composition to the emotion of the match. Players, coach, and crowd therefore occupy distinct but connected zones.



**Figure 6.** The limited 19 May follow-up subset: (a) Milliyet, (b) Fanatik, and (c) Sabah. The Fanatik scan is cropped and lower in resolution. Sources: Milliyet (2000b), Fanatik (2000b), and Sabah (2000b).

Within this three-page subset, trophy and aerial crowd photographs organize memory differently. The trophy isolates sporting achievement, while the aerial views represent scale and collective presence. In Anderson's (1995) terms, these crowd images offer a visual model of synchronized public belonging. This is a claim about representational form, not evidence that readers felt themselves part of the crowd. Sabah's greeting, Milliyet's aerial view, and Fanatik's acrostic each place a dispersed public within a single image field.

The date adds a further layer to these three pages. Because 19 May already links youth, sport, Atatürk, and the republic, the layouts can frame the victory beyond club celebration. Milliyet makes the link explicit with "ATAM işte Gençlik ve Spor" ["ATATÜRK, THIS IS YOUTH AND SPORT"]. Sabah's "ÇİFTE bayram" ["A DOUBLE CELEBRATION"] presents the UEFA victory and the national holiday as overlapping events. In this limited subset, contemporary sport is placed alongside an annual national commemoration.

## 8. Color, Mastheads, and Newspaper Identity

Yellow and red recur throughout the corpus, but they enter different brand systems and acquire different emphases. Van Leeuwen's (2011) focus on color schemes helps explain the variation. Hürriyet's corporate red merges readily with the club palette. Sabah's orange-red masthead and warm panels produce a mass-market brightness. Milliyet combines a red masthead, black vertical type, and an orange-red frame, while Cumhuriyet's black-white-red order remains more documentary. Radikal's blue logo cools its page, and Fanatik's near-total absorption of yellow and red gives it the character of a supporter object. These descriptions concern visible relationships within the supplied scans rather than calibrated historical color values.

Masthead treatment provides another marker of newspaper identity. Star places "CUP'TIK" above its logo, allowing the event to overtake the brand hierarchy. Hürriyet positions the masthead between a national headline and the trophy photograph. Akşam keeps its logo at the top but gives greater visual mass to headline and image. Milliyet makes "CANIM" nearly as prominent as the masthead, while Fanatik folds its logo and "24 sayfa" ["24 pages"]

promotion into a supporter-oriented display. For the occasion, each title adjusts the usual relation between newspaper name and lead story.

White space separates the pages just as clearly. Cumhuriyet uses it to distinguish information zones, and Radikal uses a central division to structure an argument. Sabah, Akşam, Star, Fanatik, Milliyet, and Yeni Şafak fill more of the surface with type, photographs, frames, and starbursts. That density produces urgency and recalls the visual intensity associated with tabloidization. Gencel Bek (2004) identifies related tendencies in Turkish commercial news culture, and McLachlan and Golding (2000) connect tabloidization in the British press with increased visual and human-interest content. Here, tabloid techniques operate as a flexible register available to mainstream and specialist newspapers when they seek a heightened emotional tone.

### **9. Discussion: From Analog Front Page to Digital Sports Memory**

Three overlapping configurations recur. Monumental inscription appears in Sabah, Hürriyet, Milliyet's 18 May page, and, more quietly, Cumhuriyet. Akşam, Star, Fanatik, Yeni Şafak, and Sabah's 19 May page use a pop-tabloid vocabulary that is immediate, colorful, and slogan-ready. Radikal, with Cumhuriyet to a lesser degree, preserves critical distance. Milliyet's 19 May page combines mythic treatment of Taffarel with an organized report on the urban celebration.

These configurations imply different readership positions, although no reception data are available to establish how actual readers interpreted them. Fan-oriented pages privilege saturation, chant, and souvenir value. National-mainstream pages validate pride through institutional symbols. Radikal's layout makes room for civic unease, and Yeni Şafak's design rewards recognition of European Union vocabulary. Typography and layout therefore model possible alignments between newspaper, event, and public.

Design also supplies the mechanism by which club identity is framed as national identity. The trophy photograph begins as a club sign through Galatasaray's shirts and colors. References to Turkey, flags, Atatürk silhouettes, European Union metaphors, and 19 May associations expand that frame. Billig's (1995) concept of national flagging explains the process, although the signs in this corpus are graphically emphatic. The pages make the club available as a temporary representative of the nation.

The poster-like crops, slogans, score blocks, saturated colors, and starbursts share formal features with contemporary social-media victory graphics. This comparison places late-analog newspaper design alongside later digital conventions without proposing a direct line of influence (Ritchin, 2009). The corpus does not establish that readers saved, displayed, or recirculated the pages. Their composition nevertheless affords uses beyond immediate reading, including display and souvenir circulation.

A headline can function as an explanatory label and a memory device. "CUP'TIK," "İŞTE TARİH BÖYLE YAZILIR," "YAŞAYIN VAROLUN," and "SEN İLAHSIN" are concise and designed for recall. Their mnemonic potential lies in brevity, scale, and close integration with photographs. The analysis can identify that formal affordance, although the corpus does not show which slogans readers later remembered.

## 10. Conclusion

Across the nine 18 May pages and the three-page 19 May subset, Galatasaray's UEFA Cup victory appears in sharply different visual forms. Akşam gives disbelief a yellow-red voice, Sabah moves between monumental history and a crowd-centered greeting, Star builds a popular pun, and Fanatik adopts the density of a supporter poster. Yeni Şafak turns European Union vocabulary into a score, Hürriyet places the event inside a national frame, Cumhuriyet preserves a restrained record, Radikal complicates celebration with civic disorder, and Milliyet combines affection, myth, and urban documentation. The differences confirm that layout is an interpretive practice rather than a neutral container.

Reading typography together with page position clarifies how these layouts argue. Type gives the pages registers of prayer, chant, inscription, humor, blessing, or documentary restraint. Placement lends authority according to whether the headline sits above the image, overlaps it, presses against the masthead, fills a starburst, or remains inside a grid. Color marks affiliation and sets emotional temperature. Photography supplies recurring visual material, while layout frames that material as a national trophy, an answer to Europe, a historical correction, an urban festival, a souvenir, or a civic record.

Collective memory depends on content and form. The 18 May pages and the three 19 May aftermath pages gave the victory some of its earliest durable graphic representations. Produced near the end of the analog newspaper era, they retain the authority of print and share a poster-like grammar with later digital sports media. The corpus therefore shows how a football result was organized as public history through type, image, color, and page space.

## Declarations

### *Ethics Statement*

This study does not require ethical approval as it does not include any clinical or experimental studies on humans or on animals.

### *Conflict of Interest*

The author declares that there is no conflict of interest.

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RESEARCH ARTICLE

Perceived Autism Knowledge, Attitudes, and Preparedness Among Public Service Personnel: A Cross-Sectional Training Needs Assessment

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ABSTRACT

Public service personnel are a primary point of contact for autistic citizens seeking public services, yet they remain largely unexamined in the Turkish literature. This cross-sectional study surveyed 115 public personnel in İzmir, Türkiye (response rate = 31.9%; mean age = 35.06 years; 68.7% male) using a researcher-developed self-report questionnaire assessing self-perceived ASD knowledge across six domains, four single-item affective and readiness indicators, and training preferences. Self-perceived knowledge was uniformly low (study-specific composite  $M = 1.85$ ,  $SD = 0.91$  on a 5-point scale), lowest for legal rights, where 78.3% rated themselves in the bottom two categories. Self-rated empathy ( $M = 3.42$ ) and attitude ( $M = 3.34$ ) were higher, while only 25.2% reported feeling prepared to work with autistic individuals. Contact frequency was associated with self-perceived knowledge ( $p = .52$ ) but not with self-rated empathy or attitude. In a hierarchical regression, attitude ( $\beta = .50$ ) and awareness of difficulties ( $\beta = .28$ ) were independently associated with self-perceived preparedness, whereas self-perceived knowledge was not ( $\beta = .07$ ,  $p = .439$ ); because all measures were self-reported concurrently, these associations are not causal. Participants most often endorsed behavior management (72.2%) and diagnostic processes (70.4%) as priorities, preferred visual (73.9%) and applied (73.0%) methods, and favored short formats (43.5%). Findings indicate favorable self-rated attitudes alongside low self-perceived knowledge and preparedness, suggesting that practical, scenario-based elements may usefully complement informational and attitudinal components in future training.

**Keywords:** autism spectrum disorder; needs assessment; public service personnel; in-service training; disability-inclusive public services

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## 1. Introduction

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental condition characterized by persistent differences in social communication and interaction alongside restricted and repetitive patterns of behavior (American Psychiatric Association [APA], 2022). Prevalence estimates have risen substantially over the past two decades. In the 2022 U.S. Autism and Developmental Disabilities Monitoring (ADDM) Network surveillance data, ASD was identified in 32.2 per 1,000 children aged 8 years—approximately 1 in 31—across 16 surveillance sites (Shaw et al., 2025), up from earlier ADDM estimates, although differences in participating sites, populations, data access, and ascertainment across surveillance years mean these figures are not directly comparable over time. While this increase reflects broadened diagnostic criteria, improved case ascertainment, and heightened public awareness as much as any true change in incidence (Arvidsson et al., 2018; Lundström et al., 2015), its practical implication is unambiguous: autistic individuals are present across every segment of society, and encounters between autistic people and public institutions are now an ordinary feature of service delivery rather than an exceptional one.

Public service personnel occupy a distinctive position within this landscape, and three features justify treating them as a target group in their own right. First, the service relationship is compulsory. In domains such as healthcare, civil registration, municipal services, and policing, citizens have few or no alternative providers; an autistic person cannot simply opt out of a service encounter that is going badly. Second, public personnel exercise discretionary authority. Decisions about whether a person is granted priority access, whether an unusual behavior is treated as a support need or a compliance problem, and whether a procedure is adapted or applied rigidly rest substantially with frontline staff. Personnel knowledge therefore functions less as an individual competency and more as a structural determinant of rights access. Third, public service environments—crowded waiting halls, brightly lit corridors, and noisy security checkpoints, impose considerable sensory demands on individuals with atypical sensory processing (Robertson & Baron-Cohen, 2017), raising the likelihood of acute stress responses that untrained staff are poorly equipped to anticipate or de-escalate.

Existing evidence indicates that this preparedness is frequently absent. Studies of public-facing and criminal justice personnel report a recurring pattern in which autistic communication differences are misread as rudeness, sensory-driven behavior is interpreted as deliberate noncompliance, and support needs are reframed as disciplinary matters (Crane et al., 2016; Gardner et al., 2019). Chown (2010) documented that police officers in the United Kingdom had received little targeted preparation for interactions with autistic individuals, and further observed that officers' self-appraisals of competence may exceed their actual capability—a finding with direct measurement implications for any study relying on self-report. The downstream consequences extend beyond the individual encounter: misdirected service pathways, prolonged procedures, and avoidable crises impose additional burden on families, and family members frequently report increased caregiving stress in relation to service encounters, though the specific dynamics of public-service encounters remain under-examined (Karst & Van Hecke, 2012).

These concerns intersect with binding policy commitments. The United Nations Convention on the Rights of Persons with Disabilities (United Nations, 2006), ratified by Türkiye, establishes

accessibility of public services as a state obligation, and national legislation—Law No. 5378 on Persons with Disabilities (2005)—prohibits disability-based discrimination, requires measures to provide reasonable accommodation, and establishes accessibility obligations, including the accessibility of information services and information and communication technologies. Yet accessibility frameworks have historically privileged physical and architectural adaptation, whereas the literature increasingly identifies staff awareness as an equally constitutive component of genuine access (Krahn et al., 2015). Physical compliance without personnel awareness may produce institutions that are physically enterable yet functionally difficult to navigate.

Against this background, the Turkish literature reveals a clear gap. Research on ASD awareness in Türkiye has expanded considerably in recent years (Çağlar & Özkan, 2021), but has concentrated on parents, teachers and preservice teachers, health professionals, and general population samples (Hıdıroğlu et al., 2020; Rakap et al., 2018; Rakap et al., 2022; Tölük et al., 2021). Public service personnel—arguably the first point of contact for many autistic citizens seeking to exercise their rights—have rarely been examined as an independent target group (Karavuş et al., 2021; Rakap et al., 2022). Equally important, the majority of these studies are descriptive and cross-sectional; systematic needs assessments conducted as a precondition for program design remain scarce. This matters because adult learners engage most effectively with content that is concrete and transferable to their own experience (Knowles, 1980). In-service training content, format, and duration are therefore best derived from the expressed requirements of the target group rather than imposed by curriculum designers.

The present study addresses this gap by conducting a training needs assessment with public service personnel in Türkiye. Rather than assuming what such personnel need to know, it documents their self-appraised knowledge, affective orientation, and preparedness, and elicits their own preferences regarding training design. The following research questions guided the study:

1. What are the levels of self-perceived ASD knowledge, empathy, attitude, difficulty awareness, and preparedness reported by public service personnel?
2. Do these levels differ according to prior ASD training, gender, educational attainment, and frequency of professional contact with autistic individuals?
3. How are these dimensions interrelated, and which of them predict self-perceived preparedness for serving autistic individuals?
4. Which content areas, instructional methods, instructional materials, and training durations do personnel prioritize for a prospective in-service training program?

## **2. Method**

### ***2.1. Research Design***

This study employed a cross-sectional descriptive survey design conducted as a training needs assessment. In the present study, needs assessment refers to the systematic documentation of personnel's self-reported knowledge, preparedness, perceived training needs, and training preferences to inform future program development. Competence was not directly assessed; all

indicators are self-appraisals. The design was selected because the study's purpose was to characterize an existing state of affairs across a heterogeneous occupational population at a single point in time, and to generate empirically grounded parameters for instructional design, rather than to test the effect of an intervention.

## 2.2. Participants

Participants were public service personnel employed in various public institutions in İzmir, Türkiye. Convenience sampling was used, a non-probability approach in which data are collected from accessible individuals who consent to participate (Etikan et al., 2016). Recruitment deliberately targeted a range of public service domains in order to represent the diversity of settings in which encounters with autistic citizens may occur. Collapsed into broad categories, the sample comprised general civil servants ( $n = 35$ , 30.4%), military personnel ( $n = 23$ , 20.0%), police officers ( $n = 21$ , 18.3%), court clerks and secretaries ( $n = 13$ , 11.3%), teachers and academics ( $n = 10$ , 8.7%), library staff ( $n = 4$ , 3.5%), a data entry operator ( $n = 1$ ), and other roles ( $n = 8$ , 7.0%; e.g., driver, physiotherapist, dentist, financial adviser). Categories were combined at a broad level given the small numbers in several occupations.

Of the 360 personnel invited to participate, 115 provided usable responses, yielding a response rate of 31.9%. Participants ranged in age from 20 to 55 years ( $M = 35.06$ ,  $SD = 6.70$ ), with 76.5% falling between 28 and 42 years. The sample was predominantly male ( $n = 79$ , 68.7%) and most participants were married ( $n = 77$ , 67.0%). A large majority reported no prior ASD-related training ( $n = 105$ , 91.3%), and 79.1% ( $n = 91$ ) reported never or rarely communicating directly with autistic individuals in their professional role. Nine participants (7.8%) reported having a relative or acquaintance with ASD. Prior ASD-related training was assessed using a yes/no item and therefore did not distinguish training experiences according to their content, duration, recency, quality, or intensity. The response rate of 31.9% reflects the proportion of invited personnel who submitted a completed questionnaire; the possibility of non-response bias is considered in the limitations. Full participant characteristics are presented in Table 1.

**Table 1** Participant Characteristics ( $N = 115$ )

| Variable               | Category          | n  | %    |
|------------------------|-------------------|----|------|
| Gender                 | Male              | 79 | 68.7 |
|                        | Female            | 36 | 31.3 |
| Age group (years)      | 20–27             | 14 | 12.2 |
|                        | 28–34             | 46 | 40.0 |
|                        | 35–42             | 42 | 36.5 |
|                        | 43–55             | 13 | 11.3 |
|                        |                   |    |      |
| Marital status         | Married           | 77 | 67.0 |
|                        | Single            | 38 | 33.0 |
| Educational attainment | Bachelor's degree | 68 | 59.1 |
|                        | Associate degree  | 19 | 16.5 |
|                        | Master's degree   | 15 | 13.0 |
|                        | High school       | 10 | 8.7  |
|                        | Doctorate         | 2  | 1.7  |

|                             |                         |     |      |
|-----------------------------|-------------------------|-----|------|
|                             | Primary education       | 1   | 0.9  |
| Prior ASD training          | No                      | 105 | 91.3 |
|                             | Yes                     | 10  | 8.7  |
| Professional contact with   | Never / very rarely (1) | 91  | 79.1 |
| autistic individuals        | Rarely (2)              | 11  | 9.6  |
|                             | Occasionally (3)        | 6   | 5.2  |
|                             | Often (4)               | 1   | 0.9  |
|                             | Very often (5)          | 6   | 5.2  |
| Relative/acquaintance       | Yes                     | 9   | 7.8  |
| with ASD                    | No                      | 106 | 92.2 |
| Perceived need for training | Yes                     | 101 | 87.8 |
|                             | No                      | 14  | 12.2 |

*Note.* Age:  $M = 35.06$ ,  $SD = 6.70$ , range = 20–55. There were no missing data.

### 2.3. Instrumentation

Two instruments were used: a personal information form and the Needs Assessment Questionnaire on ASD Awareness Among Public Service Personnel.

*Personal information form.* Developed by the researchers, this form collected data on age, gender, marital status, educational attainment, occupational role, prior ASD-related training, presence of a relative or acquaintance with ASD, and frequency of professional contact with autistic individuals.

*Needs Assessment Questionnaire.* The questionnaire was developed by the researchers for the present study and was constructed in two stages. In the first stage, national and international literature on ASD awareness, barriers encountered by autistic individuals in public service settings, and in-service training needs was reviewed to generate an initial item pool (Crane et al., 2016; Dillenburger et al., 2013; Rakap et al., 2022). The pool was organized around the constructs that appear in the final instrument: self-perceived knowledge, affective and readiness indicators (empathy, attitude, awareness of difficulties, preparedness), perceived training need and expected utility, and training preferences (content, materials, methods, and duration). In the second stage, the draft instrument was submitted to three academic experts holding doctoral degrees in special education, who evaluated each item for (a) comprehensibility, (b) clarity of expression, (c) adequacy of representation of the target construct, and (d) content coverage. Items judged ambiguous were simplified and items judged outside scope were removed in accordance with expert feedback. Although the questionnaire underwent expert review, it was not piloted with members of the target population before data collection, which limits conclusions concerning how consistently respondents interpreted the items. The full item wording and response anchors are provided in the Appendix.

The final instrument comprised three sections. The first assessed self-perceived knowledge across six ASD-related domains (general knowledge of ASD, diagnostic processes, characteristic features, areas of difficulty, educational processes, and legal rights and regulations) on a 5-point Likert-type scale ranging from 1 (very low) to 5 (very high). The

second assessed four affective and readiness dimensions (empathy, attitude, awareness of potential difficulties, and felt preparedness), each with a single item on the same 5-point scale, together with a single item on perceived training necessity (yes/no) and one on expected practical utility of training (1–5). Because empathy, attitude, awareness of difficulties, preparedness, and expected utility were each measured with a single item, these indicators do not permit internal-consistency estimation and provide limited construct coverage; this is noted as a limitation. The third section elicited training design preferences through multiple-response items covering content areas (seven options), instructional materials (five options), and instructional methods (six options), and a single-response item on preferred training duration.

Because all knowledge indicators were self-appraisals rather than performance-based measures, they are reported throughout as self-perceived knowledge, and self-appraisals may diverge from demonstrated knowledge (Chown, 2010). A study-specific perceived-knowledge summary index was calculated by averaging the six domain ratings. To examine whether averaging was empirically justified, an exploratory factor analysis of the six items was conducted (see Section 2.5). The index provides a parsimonious summary of participants' self-appraisals but is not presented as a validated unidimensional scale, and the six domain-level ratings are retained as primary throughout the results.

#### **2.4. Procedure**

Data were collected between March 29 and November 6, 2025 via an online questionnaire distributed to public institutions in İzmir. Participants received written information about the purpose of the study, the voluntary nature of participation, and the anonymity of responses, and provided informed consent before proceeding. The online form required a response to each item before submission, so submitted questionnaires contained no missing data; only completed submissions entered the dataset. Participants could discontinue participation at any time before submitting the questionnaire. Because submitted responses were anonymous and could not be individually identified, withdrawal was not possible after submission. No incentives were offered.

#### **2.5. Data Analysis**

Distributional assumptions were examined through Shapiro–Wilk tests and skewness and kurtosis values; single-item ordinal indicators were analyzed non-parametrically. To assess whether the six perceived-knowledge domains could be summarized as a single index, an exploratory factor analysis (principal-axis extraction) was conducted on the six items, preceded by the Kaiser–Meyer–Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity. Internal consistency of the resulting index was evaluated via Cronbach's  $\alpha$ .

Descriptive statistics addressed Research Question 1. Group comparisons for Research Question 2 employed Mann–Whitney U tests for dichotomous grouping variables, with effect sizes reported as  $r = Z/\sqrt{N}$ , and Kruskal–Wallis H tests for educational attainment, with  $\epsilon^2$  as the effect size estimate. Because educational attainment categories were sparsely populated at the extremes, they were collapsed into four groups for inferential comparison: high school or below ( $n = 11$ ), associate ( $n = 19$ ), bachelor's ( $n = 68$ ), and postgraduate ( $n = 17$ ). For Research Question 3, Spearman rank-order correlations were computed among the indicators, followed by a hierarchical multiple regression predicting self-perceived preparedness. Although

preparedness was measured using a five-category response scale, it was treated as approximately continuous in the regression; linearity and homoscedasticity were evaluated by inspection of residual-versus-fitted plots and normality of residuals by the Shapiro–Wilk test, and absence of multicollinearity was confirmed (all  $VIF < 5$ ) before interpretation. The ordinal, single-item nature of the outcome is acknowledged as a limitation. Variables were entered in three steps: demographic variables (age, gender) first as background covariates, followed by experience and perceived-knowledge variables (prior training, contact frequency, perceived-knowledge index), and then affective variables (empathy, attitude, awareness of difficulties), to examine their incremental associations with self-perceived preparedness. Gender was coded with male as the reference category and prior training with “no prior training” as the reference; contact frequency was entered as a numerical score ranging from 1 to 5. For Research Question 4, Cochran’s Q tests examined whether endorsement rates differed across the multiple-response preference options. Statistical significance was set at  $\alpha = .05$ . Effect sizes are reported for the group-comparison tests where applicable ( $r$  for Mann–Whitney U,  $\epsilon^2$  for Kruskal–Wallis). There were no missing data. Analyses beyond the primary domain-level descriptives and the preparedness regression (specifically the subgroup comparisons, correlations, and preference contrasts) are treated as exploratory.

## 2.6. Ethical Considerations

Ethical approval was granted by the Scientific Research and Publication Ethics Committee for Social and Human Sciences of İzmir Demokrasi University (Protocol No. 2025/01; Decision No. 2025/01-20; January 8, 2025), prior to the commencement of data collection. The study was conducted in accordance with the principles of the Declaration of Helsinki (World Medical Association, 2013) and institutional research ethics guidelines. All participants provided informed consent, and data were anonymized at the point of collection in accordance with Personal Data Protection Law No. 6698. Although autistic individuals were not participants in this study, they constitute its subject matter; accordingly, all instrument wording and reporting language was reviewed to avoid stigmatizing framing and to adopt a rights-based orientation (Cascio et al., 2020). Identity-first terminology is used in line with prevailing community preference and current guidance on non-ableist language in autism research (Bottema-Beutel et al., 2021). Raw data are stored on a password-protected institutional server for five years, after which they will be irreversibly deleted.

## 3. Results

### 3.1. Perceived Knowledge, Affective Orientation, and Preparedness

The six perceived-knowledge items were suitable for factor analysis ( $KMO = .89$ ; Bartlett’s test,  $\chi^2(15) = 750.3$ ,  $p < .001$ ). Exploratory factor analysis returned a single factor with an eigenvalue above 1 (4.91; next eigenvalue 0.42), accounting for 81.7% of the variance, with loadings from .83 to .95. Internal consistency was high ( $\alpha = .955$ , 95%  $CI [.940, .966]$ ; corrected item–total correlations .76 to .92). On this basis the six items were averaged into a study-specific perceived-knowledge index, reported alongside the six domain-level ratings, which remain primary. The high  $\alpha$  is consistent with a narrow, closely related set of self-appraisals and should not be read as evidence of a validated scale.

Descriptive statistics are presented in Table 2. Perceived knowledge was uniformly low: item means ranged from 1.69 to 2.00 on a 5-point scale, and the composite mean was 1.85 ( $SD = 0.91$ ). Across every domain, the majority of participants rated themselves in the lowest two response categories. The most pronounced deficit concerned legal rights and regulations ( $M = 1.69$ ,  $SD = 0.93$ ), where 78.3% rated their knowledge as low or very low and only 5.2% as high or very high, followed by diagnostic processes ( $M = 1.74$ ; 76.5% low) and educational processes ( $M = 1.81$ ; 74.8% low).

Affective and readiness indicators diverged sharply from this pattern. Empathy toward autistic individuals ( $M = 3.42$ ,  $SD = 1.42$ ) and attitude toward working with them ( $M = 3.34$ ,  $SD = 1.27$ ) were substantially higher, with 53.0% and 41.7% respectively rating themselves in the upper two categories. Preparedness, however, was low ( $M = 2.67$ ,  $SD = 1.31$ ): 46.1% did not feel prepared to work with autistic individuals, while only 25.2% did. Awareness of potential difficulties occupied an intermediate position ( $M = 2.82$ ,  $SD = 1.40$ ). Expectations regarding the practical utility of training were the highest of any indicator ( $M = 3.61$ ,  $SD = 1.23$ ), with 54.8% anticipating high or very high field utility. Consistent with this pattern, 87.8% ( $n = 101$ ) indicated that they needed training on ASD.

**Table 2** Descriptive Statistics for Perceived Knowledge and Affective Dimensions ( $N = 115$ )

| Dimension                     | M    | SD   | Mdn | Low (1–2) % | High (4–5) % |
|-------------------------------|------|------|-----|-------------|--------------|
| General knowledge of ASD      | 1.93 | 1.05 | 2.0 | 67.8        | 7.0          |
| Diagnostic processes          | 1.74 | 0.94 | 1.0 | 76.5        | 5.2          |
| Characteristic features       | 1.94 | 1.05 | 2.0 | 69.6        | 7.8          |
| Areas of difficulty           | 2.00 | 1.09 | 2.0 | 67.8        | 9.6          |
| Educational processes         | 1.81 | 1.00 | 1.0 | 74.8        | 7.0          |
| Legal rights and regulations  | 1.69 | 0.93 | 1.0 | 78.3        | 5.2          |
| Perceived knowledge composite | 1.85 | 0.91 | 1.7 | 63.5        | 2.6          |
| Empathy                       | 3.42 | 1.42 | 4.0 | 26.1        | 53.0         |
| Attitude                      | 3.34 | 1.27 | 3.0 | 22.6        | 41.7         |
| Awareness of difficulties     | 2.82 | 1.40 | 3.0 | 44.3        | 30.4         |
| Preparedness                  | 2.67 | 1.31 | 3.0 | 46.1        | 25.2         |
| Expected utility of training  | 3.61 | 1.23 | 4.0 | 18.3        | 54.8         |

*Note.* All items were rated on a 5-point scale from 1 (very low) to 5 (very high).

### 3.2. Group Differences

Shapiro–Wilk tests indicated departures from normality for all indicators ( $p < .001$ ); non-parametric tests were therefore used.

*Prior training.* Comparisons involving prior training ( $n = 10$ ), personal acquaintance ( $n = 9$ ), and no perceived training need ( $n = 14$ ) are based on small, unequal groups and are reported as exploratory. Participants with prior ASD training reported higher perceived knowledge than those without ( $n = 105$ ),  $Mdn = 3.08$  versus 1.50,  $U = 871.0$ ,  $Z = 3.43$ ,  $p < .001$ ,  $r = .32$ , along with higher awareness of difficulties ( $Z = 2.23$ ,  $p = .023$ ,  $r = .21$ ) and preparedness ( $Z = 2.24$ ,  $p = .022$ ,  $r = .21$ ). Empathy and attitude did not differ ( $ps > .26$ ).

*Professional contact.* Professional contact frequency was associated with self-perceived knowledge,  $\rho = .52, p < .001$ , and more weakly with preparedness ( $\rho = .25, p = .006$ ), awareness of difficulties ( $\rho = .22, p = .018$ ), and expected utility of training ( $\rho = .32, p < .001$ ). It was not significantly associated with empathy ( $\rho = .12, p = .223$ ) or attitude ( $\rho = .10, p = .314$ ). The questionnaire measured contact frequency but not the quality, duration, context, or voluntariness of contact.

*Personal acquaintance.* Participants reporting a relative or acquaintance with ASD ( $n = 9$ ) reported higher empathy ( $Z = 2.41, p = .014, r = .22$ ) and greater awareness of difficulties ( $Z = 2.76, p = .005, r = .26$ ), but did not differ in perceived knowledge ( $p = .704$ ).

*Educational attainment.* Educational-attainment groups differed overall in awareness of difficulties,  $H(3) = 14.06, p = .003, \epsilon^2 = .100$ . Descriptively, the postgraduate group had the highest median ( $Mdn = 4.00$ ) and the associate-degree and lower-education groups the lowest ( $Mdn = 2.00$ ), although pairwise group differences were not tested. Preparedness did not differ significantly by education,  $H(3) = 7.56, p = .056$ , and neither did perceived knowledge,  $H(3) = 3.79, p = .285$ .

*Gender.* No significant gender differences emerged on any indicator (all  $ps > .05$ ).

*Perceived need for training.* The small subgroup reporting no perceived need for training ( $n = 14$ ) also reported less favorable attitudes ( $Mdn = 1.50$  vs.  $3.00; Z = 3.24, p < .001, r = .30$ ) and lower expected utility of training ( $Mdn = 2.00$  vs.  $4.00; Z = 3.56, p < .001, r = .33$ ); they did not differ in perceived knowledge ( $p = .116$ ). Given the subgroup size and self-report design, this finding is exploratory and does not establish why these participants reported not needing training.

### 3.3. Predicting Self-Perceived Preparedness

Spearman correlations (Table 3) indicated that preparedness was most strongly associated with attitude ( $\rho = .66, p < .001$ ), awareness of difficulties ( $\rho = .56, p < .001$ ), and empathy ( $\rho = .52, p < .001$ ), and only moderately with perceived knowledge ( $\rho = .38, p < .001$ ).

**Table 3** Spearman Rank-Order Correlations Among Study Variables ( $N = 115$ )

| Variable                     | 1     | 2     | 3     | 4     | 5     | 6     |
|------------------------------|-------|-------|-------|-------|-------|-------|
| 1. Perceived knowledge       | —     |       |       |       |       |       |
| 2. Empathy                   | .37** | —     |       |       |       |       |
| 3. Attitude                  | .15   | .38** | —     |       |       |       |
| 4. Awareness of difficulties | .52** | .59** | .28** | —     |       |       |
| 5. Preparedness              | .38** | .52** | .66** | .56** | —     |       |
| 6. Expected utility          | .23*  | .46** | .40** | .22*  | .31** | —     |
| 7. Contact frequency         | .52** | .12   | .10   | .22*  | .25** | .32** |

Note. \* $p < .05$ . \*\* $p < .01$ .

A hierarchical multiple regression was conducted to identify the relative contribution of these dimensions. Assumptions were satisfied: residuals were normally distributed ( $W = .983, p = .145$ ), Durbin–Watson = 1.98, and all VIF values were below 2.1.

Demographic variables entered at Step 1 explained negligible variance,  $R^2 = .014$ ,  $F(2, 112) = 0.79$ ,  $p = .457$ . Adding prior training, contact frequency, and perceived knowledge at Step 2 produced a significant increment,  $\Delta R^2 = .153$ ,  $F(3, 109) = 6.68$ ,  $p < .001$ . Adding empathy, attitude, and awareness of difficulties at Step 3 produced a substantially larger increment,  $\Delta R^2 = .450$ ,  $F(3, 106) = 41.59$ ,  $p < .001$ , yielding a final model accounting for 61.7% of the variance in preparedness,  $F(8, 106) = 21.37$ ,  $p < .001$ , adjusted  $R^2 = .588$ .

In the final model, perceived knowledge was not significantly associated with preparedness ( $\beta = .07$ ,  $p = .439$ ). Attitude ( $\beta = .50$ ,  $p < .001$ ) and awareness of difficulties ( $\beta = .28$ ,  $p < .001$ ) were each independently associated with self-perceived preparedness. Empathy was not a significant predictor ( $\beta = .15$ ,  $p = .064$ ), and neither prior training ( $\beta = .06$ ,  $p = .411$ ) nor contact frequency ( $\beta = .06$ ,  $p = .432$ ) was independently associated with preparedness once affective variables were included. Because all predictors and the outcome were self-reported concurrently, these coefficients represent conditional associations rather than evidence that any variable determines preparedness, and the substantial explained variance should be interpreted cautiously given possible conceptual overlap among the self-report constructs.

**Table 4** Hierarchical Multiple Regression Predicting Self-Perceived Preparedness ( $N = 115$ )

| Predictor                 | B      | SE    | $\beta$ | p      | 95% CI          |
|---------------------------|--------|-------|---------|--------|-----------------|
| Age                       | -0.003 | 0.013 | -.02    | .811   | [-0.028, 0.022] |
| Gender (female)           | -0.172 | 0.181 | -.06    | .347   | [-0.531, 0.188] |
| Prior ASD training        | 0.260  | 0.314 | .06     | .411   | [-0.364, 0.883] |
| Contact frequency         | 0.079  | 0.101 | .06     | .432   | [-0.120, 0.279] |
| Perceived knowledge       | 0.095  | 0.123 | .07     | .439   | [-0.148, 0.339] |
| Empathy                   | 0.138  | 0.074 | .15     | .064   | [-0.008, 0.285] |
| Attitude                  | 0.512  | 0.069 | .50     | < .001 | [0.375, 0.649]  |
| Awareness of difficulties | 0.258  | 0.075 | .28     | < .001 | [0.109, 0.406]  |

Note.  $R^2 = .617$ , adjusted  $R^2 = .588$ ,  $F(8, 106) = 21.37$ ,  $p < .001$ . Step 1 (demographics)  $R^2 = .014$ ; Step 2  $\Delta R^2 = .153$ ,  $p < .001$ ; Step 3  $\Delta R^2 = .450$ ,  $p < .001$ .

### 3.4. Training Design Preferences

Endorsement rates differed across the content options, Cochran's  $Q(6) = 98.53$ ,  $p < .001$ . Behavior management techniques (72.2%) and diagnostic processes (70.4%) had the highest descriptive endorsement rates, followed by family and environmental support (62.6%); accommodations and modifications had the lowest (25.2%).

For instructional materials,  $Q(4) = 45.80$ ,  $p < .001$ : training seminars (62.6%) and videos and interactive content (59.1%) predominated over online courses (46.1%), workshops (36.5%), and books and articles (27.0%). For instructional methods,  $Q(5) = 123.93$ ,  $p < .001$ : visual learning (73.9%) and applied, experiential learning (73.0%) were endorsed by roughly three quarters of participants, substantially exceeding auditory learning (42.6%), group discussion (38.3%), drama and empathy activities (34.8%), and role-play (27.0%).

Regarding duration, 43.5% ( $n = 50$ ) preferred short 1–2 hr sessions, 23.5% ( $n = 27$ ) a multi-week program, 18.3% ( $n = 21$ ) a single comprehensive day, and 13.9% ( $n = 16$ ) a 6–8 hr format;

one respondent selected an “undecided” option (0.9%), so duration percentages are computed over all 115 respondents.

**Table 5** *Training Design Preferences (N = 115)*

| Preference domain and option         | n  | %    |
|--------------------------------------|----|------|
| Content areas                        |    |      |
| Behavior management techniques       | 83 | 72.2 |
| Diagnostic process of ASD            | 81 | 70.4 |
| Family and environmental support     | 72 | 62.6 |
| Instructional methods and strategies | 57 | 49.6 |
| Legal rights and regulations         | 56 | 48.7 |
| Vocational training and employment   | 56 | 48.7 |
| Accommodations and modifications     | 29 | 25.2 |
| Instructional materials              |    |      |
| Training seminars                    | 72 | 62.6 |
| Videos and interactive content       | 68 | 59.1 |
| Online courses                       | 53 | 46.1 |
| Workshops and group activities       | 42 | 36.5 |
| Books and articles                   | 31 | 27.0 |
| Instructional methods                |    |      |
| Visual learning                      | 85 | 73.9 |
| Applied and experiential learning    | 84 | 73.0 |
| Auditory learning                    | 49 | 42.6 |
| Group discussion and interaction     | 44 | 38.3 |
| Drama and empathy activities         | 40 | 34.8 |
| Role-play activities                 | 31 | 27.0 |
| Preferred duration                   |    |      |
| Short sessions (1–2 hr)              | 50 | 43.5 |
| Long-term program (several weeks)    | 27 | 23.5 |
| One full comprehensive day           | 21 | 18.3 |
| Medium-length sessions (6–8 hr)      | 16 | 13.9 |
| Undecided                            | 1  | 0.9  |

*Note.* Content areas, materials, and methods were multiple-response items; percentages therefore exceed 100 within each domain. Cochran's  $Q$ : content  $Q(6) = 98.53, p < .001$ ; materials  $Q(4) = 45.80, p < .001$ ; methods  $Q(5) = 123.93, p < .001$ . Duration was a single-response item.

#### 4. Discussion

This study examined the ASD-related training needs of public service personnel in Türkiye, a workforce that constitutes a primary point of contact for autistic citizens seeking access to public services yet remains largely unexamined in the national literature. Three findings warrant particular attention: the uniformly low level of perceived knowledge, the marked dissociation between affective orientation and felt preparedness, and the finding that preparedness was predicted by attitudinal rather than knowledge-related variables.

#### ***4.1. A Knowledge Floor, Sharpest Where Rights Are at Stake***

Perceived knowledge was low across all six domains examined, with the composite mean falling below 2 on a 5-point scale and 91.3% of participants reporting no prior ASD training of any kind. This pattern is consistent with earlier Turkish findings documenting limited ASD knowledge among various occupational groups (Gürbüz Özgür et al., 2019; Rakap et al., 2022) and with international evidence from public safety contexts (Chown, 2010).

The distribution of these self-ratings is more informative than their overall magnitude. Self-appraised knowledge was lowest for legal rights and regulations, where 78.3% of participants rated themselves in the bottom two categories and only 5.2% in the top two. Türkiye's ratification of the Convention on the Rights of Persons with Disabilities (United Nations, 2006) and the provisions of Law No. 5378 (2005) establish entitlements, including procedural accommodation and accessible communication, whose implementation depends in part on frontline personnel being aware that such entitlements exist. Limited self-perceived knowledge of legal rights may create barriers to their consistent implementation, although actual legal knowledge and service practices were not assessed in this study. This pattern is consistent with the argument that staff awareness is a component of accessibility rather than a supplement to physical adaptation (Krahn et al., 2015).

These are self-appraisals rather than demonstrated knowledge, and self-ratings may diverge from performance in either direction (Chown, 2010). We therefore restrict interpretation to what participants reported about themselves. How self-perceived knowledge relates to actual service behavior was not assessed here and would require behavioral or observational data to establish.

#### ***4.2. Favorable Attitudes Alongside Low Self-Perceived Knowledge***

The second finding concerns the divergence between affective and competence-related indicators. Participants rated their empathy toward autistic individuals ( $M = 3.42$ ) and their attitude toward working with them ( $M = 3.34$ ) substantially higher than their knowledge, and 54.8% anticipated that training would be of high practical utility. Yet only 25.2% felt prepared to work with autistic individuals, and 46.1% explicitly did not.

This configuration, favorable self-rated attitudes alongside low self-perceived knowledge and preparedness, suggests a possible focus for future training. Studies of public-facing personnel have documented misattributions in which autistic communication differences are read as rudeness and sensory-driven behavior as deliberate noncompliance (Crane et al., 2016; Gardner et al., 2019), though whether the present sample would show such patterns in practice was not assessed. To the extent that these participants already report favorable attitudes, future programs for similar groups might place relatively more emphasis on concrete, applicable knowledge than on attitude change, a hypothesis that intervention research could test directly.

From a program design standpoint, this pattern points to a possible focus. Future programmes for similar samples may place greater emphasis on concrete, situationally applicable content while retaining appropriate informational and attitudinal components. The relative effectiveness of these elements was not evaluated in the present study and would need to be established through intervention research.

### 4.3. Factors Associated with Self-Perceived Preparedness

The hierarchical regression sharpened this picture considerably. Demographic characteristics explained essentially no variance in preparedness. Experience and knowledge variables added a modest increment. Affective variables added a substantial one, producing a final model that accounted for 61.7% of the variance. Within that model, attitude ( $\beta = .50$ ) and awareness of potential difficulties ( $\beta = .28$ ) emerged as significant predictors, while perceived knowledge did not ( $\beta = .07, p = .439$ ).

Two readings of this non-significant association can be distinguished. The first is substantive: self-perceived preparedness may be associated more closely with disposition and with anticipatory understanding of what could go wrong than with declarative knowledge about ASD. On this reading, awareness training built solely around information transmission might be less well targeted than training that also addresses scenario-based anticipation of difficulty; this is a hypothesis for future evaluation rather than a demonstrated result, since the study did not compare training approaches.

The second reading is methodological and equally plausible: self-perceived knowledge in this sample was compressed near the floor of the scale ( $M = 1.85, SD = 0.91$ , with 63.5% in the bottom two categories), and a predictor with restricted variance may fail to differentiate outcomes regardless of its underlying importance. The cross-sectional design cannot adjudicate between these interpretations. In the final model, attitude and awareness of potential difficulties were the indicators independently associated with self-perceived preparedness; because all constructs were measured concurrently by self-report and attitude and preparedness overlap conceptually (see Section 4.7), these associations should not be read as evidence that attitude or awareness determines preparedness. Whether knowledge would be associated with preparedness in a sample with greater knowledge variance remains an open question.

Awareness of potential difficulties merits separate comment, since it was the only dimension to differ significantly by educational attainment and one of only two to differ by personal acquaintance with an autistic individual. It appears to function as a bridging construct between disposition and competence, an appreciation that the encounter will present specific challenges, without necessarily knowing how to meet them. Its predictive weight suggests it is a productive explicit target for instructional design rather than an incidental byproduct.

### 4.4. Professional Contact and Self-Rated Attitudes

Professional contact frequency was associated with self-perceived knowledge ( $p = .52$ ) but not with self-rated empathy ( $p = .12$ ) or attitude ( $p = .10$ ). Intergroup contact is generally expected to improve attitudes, and studies in campus and educational settings have reported associations between personal contact and more favorable ASD-related orientations (Dillenburger et al., 2017; Tipton & Blacher, 2014). One possible explanation for the present pattern is that professional and personal contacts differ in their quality or context. However, this study measured contact frequency rather than these characteristics, so this interpretation remains speculative. Differences between professional and personal forms of contact may warrant examination in future research; in the present data, participants with a personal relative or acquaintance with ASD reported higher empathy and difficulty awareness, though not higher knowledge.

Because the study did not manipulate or measure the nature of contact, it cannot establish whether professional exposure contributes to attitudinal change. This question is better addressed by designs that characterize the quality and context of contact directly.

#### ***4.5. The Subgroup Reporting No Perceived Training Need***

A small subgroup ( $n = 14$ , 12.2%) reported not needing ASD training. These participants did not differ from the remainder in perceived knowledge but reported less favorable attitudes ( $r = .30$ ) and lower expectations of training utility ( $r = .33$ ). The data show lower attitudes and expected utility in this subgroup; they do not establish disengagement, poorer future service encounters, or a need for mandatory training. One implication worth exploring is that voluntary programs may under-reach personnel with less favorable initial attitudes, though testing this would require follow-up on who enrolls and who benefits.

#### ***4.6. Design Preferences and What They Reveal***

Preference data yielded clear and statistically differentiated priorities. Participants prioritized behavior management techniques (72.2%) and diagnostic processes (70.4%), preferred visual (73.9%) and applied experiential (73.0%) instructional methods, favored seminars and interactive video content over text-based resources, and predominantly requested short 1–2 hr formats (43.5%). The methodological preferences align closely with adult learning principles, which hold that adult learners engage most effectively with concrete, immediately transferable content (Knowles, 1980).

The content preferences may also be read more cautiously. The high endorsement of behavior management techniques alongside the lower ranking of accommodations and modifications (25.2%) is consistent with a framing in which autistic behavior is seen as something to be managed rather than as communication or as a signal that the environment could be adjusted, though the preference items do not directly establish participants' underlying models. Needs assessment data usefully inform program design without being implemented uncritically: a program could meet the expressed demand for practical behavioral guidance while situating it within an antecedent-focused, environmentally oriented approach.

A comparable tension appears in duration preferences. The strong preference for brief formats reflects the real constraints of shift-based public sector work, but is difficult to reconcile with the low level of self-perceived knowledge reported here. A modular architecture of short, self-contained sessions delivered sequentially offers a reasonable resolution, preserving both feasibility and cumulative depth.

#### ***4.7. Limitations***

Several limitations qualify these findings. The study employed a cross-sectional convenience sample drawn from a single province, and the results should not be generalized to the national public workforce. The response rate of 31.9% raises the possibility of non-response bias, and it is plausible that personnel with greater interest in ASD were more likely to participate, which would render the present estimates of knowledge and motivation optimistic rather than conservative.

All measures were self-report administered at a single time point; no performance-based assessment of ASD knowledge, behavioral measure, or service-quality outcome was collected,

so the study speaks to self-perceptions rather than demonstrated knowledge or practice, and self-appraisal may diverge from performance (Chown, 2010). Because the design is cross-sectional, all associations reported here are correlational and cannot support causal inference. The affective and readiness dimensions were each measured by a single item, precluding reliability estimation and limiting construct coverage. The perceived-knowledge composite showed very high internal consistency ( $\alpha = .955$ ), which, while satisfying conventional criteria, may indicate item redundancy and a correspondingly narrow construct (Streiner, 2003). Attitude and preparedness were substantially correlated ( $p = .66$ ), and their conceptual overlap means the regression finding should be interpreted as descriptive of shared variance rather than as evidence of causal priority.

Subgroup analyses involving participants with prior training ( $n = 10$ ) and those with a personal acquaintance with ASD ( $n = 9$ ) were underpowered and should be treated as exploratory.

Finally, and most importantly, the needs assessment consulted only service providers. Autistic individuals and their families, who experience the consequences of personnel unpreparedness directly, were not included as informants. A fuller account of what public personnel need to know would require their perspectives, and their absence constitutes a substantive limitation on the validity of the needs profile presented here.

#### ***4.8. Conclusion***

Public service personnel in this sample reported low self-perceived ASD knowledge, with the lowest self-ratings for legal rights, alongside more favorable self-rated attitudes and expectations of training utility. In the regression, self-perceived preparedness was associated with attitude and awareness of potential difficulties rather than with self-perceived knowledge, an association that is cross-sectional and not causal. These findings suggest that practical and scenario-based elements may usefully complement informational and attitudinal components in future training programs for this population, a possibility that intervention research should test directly. Future work should incorporate performance-based knowledge measures, include autistic individuals and family members as informants, examine the quality as well as the frequency of contact, and evaluate whether specific training designs produce measurable change in service encounters.

#### ***Declarations***

##### ***Author Contributions***

Kağan Gümüş (kgngms@icloud.com): conceptualization, data collection, formal analysis, writing – original draft. Emre Ünlü (eskemre@gmail.com): supervision, methodology, formal analysis, writing – review and editing. Both authors read and approved the final version of the manuscript.

##### ***Author Note***

This article reports the needs assessment phase of a broader master's thesis project conducted by the first author under the supervision of the second author at İzmir Demokrasi University. Findings concerning the effectiveness of the training program developed on the basis of this needs assessment are reported separately.

### ***Ethical Approval***

İzmir Demokrasi University, Scientific Research and Publication Ethics Committee for Social and Human Sciences (Protocol No. 2025/01; Decision No. 2025/01-20; January 8, 2025).

### ***Conflict of Interest***

The authors declare no conflict of interest.

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### ***Data Availability***

The anonymized dataset is available from the corresponding author upon reasonable request.

### ***Use of Artificial Intelligence***

The authors used AI-assisted tools for language editing and reference formatting checks. All scientific content, analytic decisions, interpretations, and final wording were determined and verified by the authors, who take full responsibility for every claim in the manuscript. AI tools were not listed as authors and were not used to generate scientific content, participants, or data.

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## Appendix. Questionnaire Items and Response Anchors

Items were administered in Turkish; English translations are provided here. Section A (perceived knowledge) and Section B (affective and readiness indicators) used a 5-point response scale; the anchors for the six knowledge items were 1 (very low), 2 (low), 3 (moderate), 4 (high), 5 (very high). Empathy, attitude, awareness of difficulties, preparedness, and expected utility each used a parallel 1 (very low) to 5 (very high) anchor. Perceived training need was a yes/no item. Section C (preferences) used the response options listed in Table 5.

**Section A — Self-perceived knowledge (rate your level of knowledge regarding ...):** (1) autism spectrum disorder (ASD) in general; (2) the ASD diagnostic process; (3) the characteristic features of individuals with ASD; (4) the areas of difficulty experienced by individuals with ASD; (5) the educational processes of individuals with ASD; (6) the legal rights of individuals with ASD.

**Section B — Affective and readiness indicators:** (7, empathy) Rate your level of empathy toward individuals with ASD. (8, attitude) Rate your attitude toward working with individuals

with autism. (9, awareness of difficulties) Rate how aware you are of the difficulties you might experience when encountering an individual with ASD. (10, preparedness) How prepared do you feel to work with individuals with ASD? (11, perceived need) Do you think you need training about ASD? [yes/no] (12, expected utility) To what extent do you think training about individuals with autism would be useful to you in the field?

**Section C — Training preferences:** (13) On which topics about ASD would you like more information? [multiple response] (14) Which training materials or resources would you prefer for learning about ASD? [multiple response] (15) Which instructional methods would you like a training program on ASD to include? [multiple response] (16) What do you think about the duration of the training program? [single response] (17) Please state the reasons for your duration preference. [open-ended] The response options for items 13–16 are reported in Table 5.

REVIEW ARTICLE

Natural Products as Multi-Target Agents in Cancer Prevention and Progression

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ABSTRACT

Plant-derived natural products have long been an invaluable source of anticancer agents for the prevention and treatment of cancer. Although numerous modern and costly treatment strategies are currently used to combat cancer, factors such as treatment resistance, systemic toxicity, and tumor heterogeneity continue to be major obstacles to successful clinical outcomes. To overcome these limitations, bioactive natural products stand out as potential therapeutic agents due to their high molecular diversity and multi-targeted biological activities. Various classes of phytochemicals, including polyphenols, flavonoids, terpenoids, and alkaloids, represent promising candidates for new complementary anticancer strategies due to their ability to simultaneously modulate multiple cellular mechanisms. This review focuses on the roles of ten bioactive compounds-curcumin, resveratrol, quercetin, epigallocatechin gallate (EGCG), sulforaphane, carvacrol, berberine, luteolin, apigenin, honokiol and propolis-which have shown efficacy in experimental and clinical settings and are among the most widely investigated compounds in contemporary research, in the context of cancer progression. This study provides an overview of the classification and mechanism-based evaluation of these compounds based on their effects on apoptosis avoidance, metastasis, epithelial-mesenchymal transition (EMT), and tumor microenvironment. Furthermore, the current opportunities and limitations of translating these compounds into clinical applications are discussed.

**Keywords:** natural products; phytochemicals; cancer hallmarks; apoptosis evasion; epithelial–mesenchymal transition; tumor microenvironment

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## 1. Introduction

Cancer remains one of the most significant global health challenges based on current data, due to its increasing incidence, complex biology, and limitations in treatment strategies (Sung et al., 2026). Worldwide, cancer ranks as the second leading cause of death. According to the latest GLOBOCAN 2024 estimates, approximately 20.6 million new cancer cases and 9.8 million cancer-related deaths were reported globally, highlighting the growing burden of cancer on health systems worldwide (Sung et al., 2026). Moreover, the global cancer burden is expected to increase substantially in the coming decades. The rise in cancer incidence is largely driven by genetic predispositions as well as modifiable risk factors, including tobacco use, a sedentary lifestyle associated with modern living, unhealthy dietary habits, and environmental pollution. The complex and molecularly intricate nature of cancer underscores the necessity for effective prevention and therapeutic strategies (Anand et al., 2008).

Cancer development and progression are governed by a complex interplay of genetic, epigenetic, and microenvironmental alterations that enable malignant cells to acquire distinct biological capabilities (Hanahan & Weinberg, 2011). The hallmarks of cancer provide a comprehensive framework for understanding these interconnected processes, including sustained proliferative signaling, resistance to cell death, metastatic progression, angiogenesis, immune evasion, and continuous remodeling of the tumor microenvironment. These interrelated mechanisms enable cancer cells to survive under adverse conditions and contribute to tumor progression and therapeutic resistance (Hanahan & Weinberg, 2011; Hanahan, 2022).

One of the most critical and challenging features of cancer cells is their ability to evade programmed cell death (apoptosis). Dysregulation of apoptotic mechanisms, including alterations in mitochondrial signaling, pro- and anti-apoptotic regulators, and caspase activation, allows tumor cells to escape normal cellular elimination processes (Fuchs & Steller, 2011). In addition, metastatic dissemination mediated through epithelial–mesenchymal transition (EMT), extracellular matrix remodeling, and angiogenic adaptation represents another key determinant of cancer progression (Pastushenko & Blanpain, 2019). Furthermore, the tumor microenvironment (comprising immune cells, stromal components, extracellular matrix, and signaling molecules) actively contributes to tumor growth, immune suppression, and therapeutic resistance (Baghban et al., 2020).

Despite significant advances in cancer therapy, limitations such as drug resistance, systemic toxicity, and tumor heterogeneity continue to constrain treatment efficacy (Vasan et al., 2019). Therefore, multi-target therapeutic approaches capable of modulating several cancer-related processes have gained increasing attention. Natural products and plant-derived bioactive compounds represent promising candidates due to their structural diversity and their ability to regulate multiple molecular and cellular mechanisms involved in cancer progression (Newman & Cragg, 2020). Phytochemicals such as polyphenols, flavonoids, terpenoids, alkaloids, and other bioactive molecules exert anticancer effects by modulating apoptosis, metastatic behavior, oxidative stress balance, inflammation, and tumor microenvironment interactions (Aggarwal & Shishodia, 2006). Unlike single-target therapeutic approaches, these compounds can simultaneously influence multiple cancer hallmarks, providing a rationale for their investigation as complementary or preventive strategies in cancer therapy (Aggarwal & Shishodia, 2006; Newman & Cragg, 2020). In this context, the molecular-level investigation of

target phytochemicals, particularly regarding their potential to suppress tumor survival pathways and reactivate apoptotic mechanisms, is of considerable importance.

In this review, ten bioactive compounds that have demonstrated substantial therapeutic potential in experimental and clinical studies and represent the most frequently researched agents in current literature (curcumin, resveratrol, quercetin, epigallocatechin gallate [EGCG], sulforaphane, carvacrol, berberine, luteolin, apigenin, and honokiol), along with propolis (a natural bee product) were examined as multi-target agents in cancer prevention and therapy strategies. Compound selection was guided by three primary inclusion criteria: (i) demonstrated evidence in experimental and/or clinical models, (ii) representation of distinct chemical classes (polyphenols, flavonoids, terpenoids, and alkaloids), and (iii) prominent coverage in current cancer literature. Conversely, the exclusion criteria were defined as compounds with insufficient experimental data, poorly defined molecular mechanisms, or efficacy strictly restricted to a single cancer cell line. These compounds were categorized based on their abilities to target apoptosis evasion, suppress metastatic and EMT-related processes, and modulate oxidative stress and tumor microenvironment dynamics.

In this review, we comprehensively summarize recent studies and mechanistic insights regarding the therapeutic potential of natural products in cancer prevention and therapy, focusing predominantly on literature published between 2010-2026 years. (pivotal older sources were also cited where appropriate). Literature searches were conducted across major electronic databases, including PubMed, Web of Science, ScienceDirect, Scopus, Google Scholar, and ClinicalTrials.gov (last accessed in July 2026) This study provides critical insights into the multi-target mechanisms and anticancer efficacy of ten selected bioactive compounds: curcumin, resveratrol, quercetin, epigallocatechin gallate (EGCG), sulforaphane, carvacrol, berberine, luteolin, apigenin, and honokiol, alongside propolis, aiming to inform future translational and clinical applications.

The review offers an integrated perspective on the anticancer potential of these agents by detailing key evidence from *in vitro*, *in vivo*, and clinical models across various malignancy types. Specifically, this work synthesizes their multi-target actions into key operational axes, including the modulation of: (I) apoptosis reactivation and survival pathway inhibition, (II) metastatic dissemination and epithelial–mesenchymal transition (EMT), (III) oxidative stress dynamics, (IV) tumor microenvironment remodeling, and (V) potential synergistic effects with conventional chemotherapeutics. Compounds were selected based on robust experimental validation, mechanistic clarity, structural diversity (encompassing polyphenols, flavonoids, terpenoids, and alkaloids), and high relevance in contemporary oncological research. Consequently, this review serves as a comprehensive resource for researchers aiming to exploit multi-target natural agents for innovative cancer treatment and prevention strategies.

## **2. Multi-Target Mechanisms of Natural Bioactive Agents in Cancer**

Natural products and plant-derived bioactive compounds offer significant therapeutic advantages in oncology because of their structural diversity and ability to simultaneously modulate multiple oncogenic signaling pathways. Rather than acting on a single molecular target, these multi-target agents exert pleiotropic effects that collectively intersect with the core hallmarks of cancer development and progression. (Newman & Cragg, 2020)

As illustrated in Figure 1, ten representative natural bioactive compounds, along with propolis, have gained prominent attention in current oncological research owing to their distinct chemical classes and multi-target capabilities.p

Cancer is not merely a disease characterized by uncontrolled cell proliferation; rather, it is a complex process that arises from the accumulation of numerous biological alterations that enable tumor cell survival, invasion of surrounding tissues, and development of therapeutic resistance. The “hallmarks of cancer” framework, a fundamental concept in understanding cancer biology, systematically defines the essential characteristics acquired by malignant cells and facilitates the understanding of the mechanisms involved in tumor development and progression (Hanahan, 2022).

Within this framework, cancer cells acquire fundamental biological capabilities, including sustained proliferative signaling, evasion of growth suppressor mechanisms, resistance to programmed cell death (apoptosis), replicative immortality, induction of angiogenesis, activation of invasion and metastasis, evasion of immune surveillance, and establishment of a tumor-supportive microenvironment (Hanahan, 2022). These characteristics do not represent independent processes; rather, they constitute a complex network of interacting mechanisms that collectively drive tumor development.

The ability of cancer cells to evade apoptotic mechanisms provides a significant advantage in the early stages of tumor development. Dysregulation of apoptotic signaling pathways, including increased expression of anti-apoptotic proteins, suppression of mitochondrial death signaling, and inhibition of caspase activation, enables cells to escape normal elimination processes (Pistritto et al., 2016). In addition, epithelial–mesenchymal transition (EMT), extracellular matrix remodeling, and angiogenic adaptations play critical roles in metastatic progression by facilitating the dissemination of cancer cells to distant tissues (Mittal, 2018).

The tumor microenvironment is a complex system comprising dynamic interactions among cancer cells, stromal cells, immune cells, extracellular matrix components, and various signaling molecules. This microenvironment supports tumor growth through chronic inflammation, immune suppression, angiogenesis, and development of therapeutic resistance (Hinshaw & Shevde, 2019). Therefore, therapeutic approaches that target multiple hallmarks of cancer have become an important area of research in contemporary cancer therapy.

### ***2.1. Natural Products as Multi-Target Therapeutic Agents***

The multifactorial and heterogeneous nature of cancer limits the effectiveness of therapeutic approaches directed toward a single molecular target. Therefore, there is growing interest in multi-target therapeutic strategies capable of regulating different biological processes. Plant-derived natural products have emerged as important candidates in cancer research because of their extensive chemical diversity and their ability to modulate multiple cellular mechanisms (Newman & Cragg, 2020).

Plant-derived bioactive compounds, including polyphenols, flavonoids, terpenoids, and alkaloids, can modulate processes that play critical roles in cancer development, such as cell proliferation, apoptosis, oxidative stress, inflammation, metastasis, and regulation of the tumor microenvironment (Šemeláková et al., 2026). Curcumin, resveratrol, quercetin, epigallocatechin gallate (EGCG), berberine, and other natural compounds have been reported

to suppress tumor progression by exerting simultaneous effects on multiple cancer hallmarks (Anand et al., 2008; Šemeláková et al., 2026).

The multi-target mechanisms of natural products offer potential advantages, particularly in overcoming major challenges in cancer treatment, including tumor heterogeneity and therapeutic resistance. However, low bioavailability, metabolic instability, and limitations associated with clinical translation remain important challenges that must be addressed for their therapeutic application (Newman & Cragg, 2020)

Therefore, investigating the regulatory effects of natural products on cancer hallmarks may contribute to the development of novel complementary therapeutic approaches for cancer prevention and the control of cancer progression.

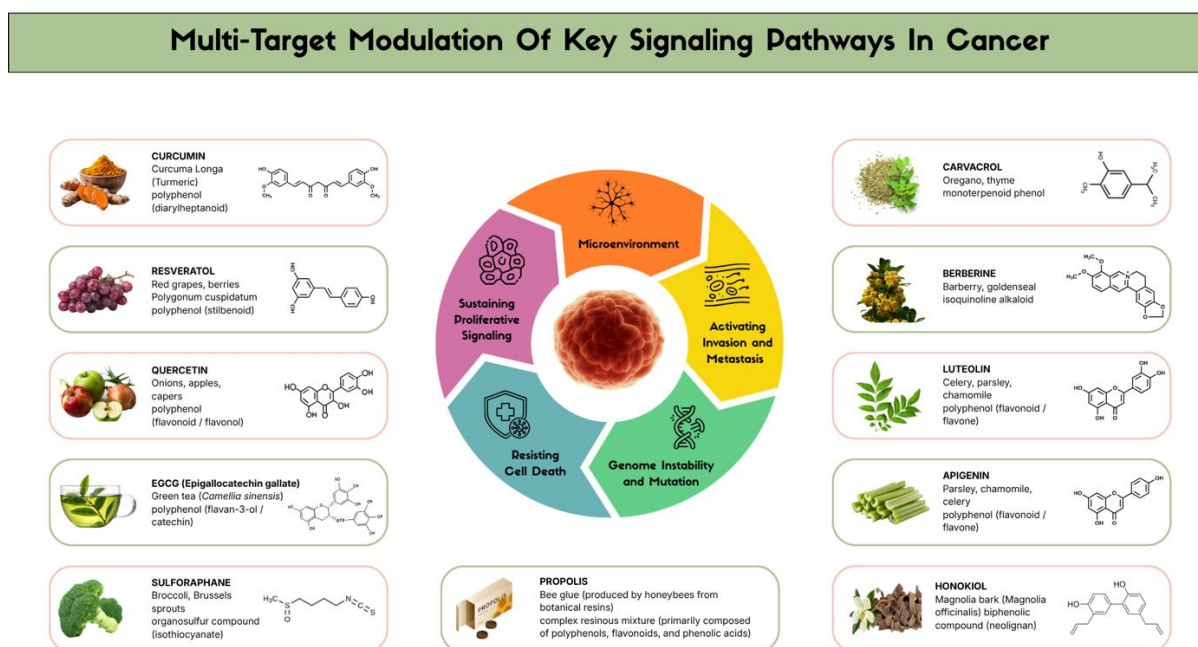


**Figure 1** Schematic overview of the ten selected natural bioactive compounds and propolis, categorized by their chemical classes, and their multi-target modulation across key functional hallmarks of cancer progression. The central diagram illustrates the five core operational axes targeted by these compounds: sustaining proliferative signaling, resisting cell death, genome instability and mutation, activating invasion and metastasis, and tumor microenvironment remodeling.

## 2.2. Natural Products Targeting Apoptosis Evasion

To systematically evaluate the anticancer potential of plant-derived natural products, ten representative bioactive compounds (curcumin, resveratrol, quercetin, EGCG, sulforaphane, carvacrol, berberine, luteolin, apigenin, and honokiol) alongside propolis were analyzed based on their distinct chemical classes and multi-target capabilities. Rather than acting via a single molecular pathway, these agents exert broad biological effects that directly intersect with major hallmarks of cancer progression, including apoptosis evasion, metastatic dissemination, genomic instability, and tumor microenvironment remodeling.

To provide a structured and comprehensive overview, the chemical classifications, primary molecular targets, key signaling cascades, and affected cancer hallmarks for each selected agent are systematically summarized in Table 1, supported by representative recent literature

**Table 1** Chemical classification, primary molecular targets, key signaling cascades, and affected cancer hallmarks of the ten selected natural bioactive compounds and propolis.

| Compound                        | Chemical Class                                                         | Primary Molecular Targets & Key Signaling                       | Cancer Hallmarks Affected                                                                                                  | References                                                                   |
|---------------------------------|------------------------------------------------------------------------|-----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Curcumin                        | Polyphenol (Diarylheptanoid)                                           | NF- $\kappa$ B, PI3K/Akt, Bcl-2 family, Caspase-3/9, XIAP       | Resisting cell death, Sustaining proliferative signaling                                                                   | Demirci et al. (2025); Farghadani & Naidu (2021)                             |
| Resveratrol                     | Polyphenol (Stilbenoid)                                                | MMP-2/9, TGF- $\beta$ , Wnt beta-catenin, COX-2                 | Activating invasion and metastasis, Sustaining proliferative signaling                                                     | Batirel et al. (2025); Ren et al. (2021); Song et al. (2019)                 |
| Quercetin                       | Polyphenol (Flavonoid / Flavonol)                                      | PI3K/Akt/mTOR axis, p53, p21/WAF1, Bad, Survivin                | Resisting cell death, Sustaining proliferative signaling                                                                   | Russo et al. (2012); Tang et al. (2020); Reyes-Farias & Carrasco-Pozo (2019) |
| EGCG (Epigallocatechin gallate) | Polyphenol (Flavan-3-ol / Catechin)                                    | ROS machinery, NF- $\kappa$ B, MMPs, Angiogenic drivers         | Genome instability and mutation, Resisting cell death                                                                      | Khan & Mukhtar (2019); Li et al. (2024); Negri et al. (2018)                 |
| Sulforaphane                    | Organosulfur compound (Isothiocyanate)                                 | Nrf2/Keap1 axis, ARE signaling, HDACs, Phase II enzymes         | Genome instability and mutation, Sustaining proliferative signaling                                                        | Su et al. (2018); Mangla et al. (2020)                                       |
| Carvacrol                       | Monoterpenoid phenol                                                   | Mitochondrial lipid bilayer, ROS generation, Cytochrome c, PARP | Resisting cell death, Sustaining proliferative signaling                                                                   | Besli et al. (2026); Sharifi-Rad et al. (2018); Khan et al. (2017)           |
| Berberine                       | Isoquinoline alkaloid                                                  | EMT transcription factors, AMPK, Cell motility machinery        | Activating invasion and metastasis, Resisting cell death                                                                   | Rauf et al. (2021); Samadi et al. (2020)                                     |
| Luteolin                        | Polyphenol (Flavonoid / Flavone)                                       | MAPK/ERK, PI3K/Akt, Snail, Twist, E-cadherin                    | Activating invasion and metastasis, Resisting cell death                                                                   | Qin et al. (2021); Imran et al. (2019)                                       |
| Apigenin                        | Polyphenol (Flavonoid / Flavone)                                       | TNFR1, Fas (CD95), DR4/DR5, Caspase-8/9/3, PARP                 | Resisting cell death, Activating invasion and metastasis                                                                   | Sung et al. (2016); Imran et al. (2020); Pan et al. (2021)                   |
| Honokiol                        | Biphenolic compound (Neolignan)                                        | STAT3, Sonic Hedgehog (Shh), Oct4, Sox2, Nanog                  | Resisting cell death, Microenvironment alterations                                                                         | Ong et al. (2020); Avtanski et al. (2014)                                    |
| Propolis                        | Complex resinous mixture (Polyphenols, flavonoids, and phenolic acids) | IL-6, NF- $\kappa$ B, VEGF, MMP-2/9, Caspases                   | Resisting cell death, Sustaining proliferative signaling, Microenvironment alterations, Activating invasion and metastasis | Sforcin (2016); Li et al. (2021); Zhu et al. (2024)                          |

### 3. Molecular Mechanisms and Hallmark-Targeted Actions of Bioactive Agents

#### 3.1. Dysregulation of Apoptotic Mechanisms in Cancer

Apoptosis is a genetically programmed cell death mechanism required for maintaining cellular homeostasis, tissue development, and removing oncogenic cells (Cavalcante et al., 2019). In malignant cells, the evasion of apoptosis drives unconstrained clonal expansion, survival under metabolic stress, and therapeutic resistance (Pistritto et al., 2016). As illustrated in Figure 2, this survival phenotype is governed by hyperactivated prosurvival signaling pathways, including Nuclear Factor-kappa B (NF- $\kappa$ B) and Phosphoinositide 3-kinase/Akt (PI3K/Akt), alongside upregulation of anti-apoptotic Bcl-2 proteins and suppression of endogenous caspase activation (Kale et al., 2018; Pfeffer & Singh, 2018).

Intrinsic apoptotic dysregulation primarily involves an altered balance between pro- and anti-apoptotic Bcl-2 family members (Kale et al., 2018). Upregulation of anti-apoptotic Bcl-2 prevents mitochondrial outer membrane permeabilization (MOMP), blocking the release of pro-apoptotic factors into the cytosol (Cavalcante et al., 2019). Concurrently, executioner caspase signaling is inhibited by inhibitor of apoptosis proteins (IAPs) and functional mutations in the TP53 tumor suppressor gene (Marei et al., 2021).

Natural bioactive compounds (specifically curcumin, carvacrol, quercetin, and apigenin) can reverse this apoptotic resistance through targeted molecular interventions (Figure 2). These agents lower mitochondrial membrane potential, stimulate cytosolic cytochrome c release, induce downstream activation of initiator caspase-9 and executioner caspase-3, and trigger DNA fragmentation, ultimately driving malignant cells toward apoptotic cell death (Pfeffer & Singh, 2018; Marei et al., 2021).

### ***3.1.1. Curcumin: Induction of Apoptosis and Prosurvival Death Signaling***

Curcumin, a natural polyphenolic diarylheptanoid derived from the rhizomes of *Curcuma longa*, induces apoptosis across various human cancer cell lines through the modulation of survival pathways and executioner apoptotic cascades (Tomeh et al., 2019; Farghadani & Naidu, 2021). The primary mechanism of curcumin-induced cell death involves the suppression of constitutive survival signaling networks. Specifically, curcumin inhibits Nuclear Factor-kappa B (NF- $\kappa$ B) and Phosphoinositide 3-kinase/Akt (PI3K/Akt) pathways, leading to the downregulation of downstream anti-apoptotic targets, including cyclin D1, c-Myc, and X-linked inhibitor of apoptosis protein (XIAP) (Demirci et al., 2025).

At the organelle level, curcumin targets mitochondrial integrity by altering the expression balance of the Bcl-2 family (Figure 2). It upregulates pro-apoptotic Bax while suppressing anti-apoptotic Bcl-2 and Bcl-xL, which leads to a loss of mitochondrial membrane potential and the subsequent cytosolic release of cytochrome c (Farghadani & Naidu, 2021). Cytosolic cytochrome c facilitates apoptosome assembly, triggering sequential cleavage and activation of initiator caspase-9 and executioner caspase-3, which culminates in nuclear DNA fragmentation (Figure 2). Additionally, curcumin promotes cell death by inducing intracellular reactive oxygen species (ROS) accumulation and activating the c-Jun N-terminal kinase (JNK) pathway, enhancing its capacity to sensitize chemoresistant tumor phenotypes to programmed cell death (Tomeh et al., 2019).

### ***3.1.2. Carvacrol: Disruption of Mitochondrial Potential and Intrinsic Death Signaling***

Carvacrol, a monoterpenoid phenol abundant in the essential oils of Lamiaceae species such as oregano and thyme, induces intrinsic apoptosis in cancer cells through mitochondrial membrane disruption (Besli et al., 2026; Khan et al., 2017). Due to its lipophilic structure, carvacrol integrates into cellular membranes and targets the inner mitochondrial membrane, causing a loss of mitochondrial membrane potential (Figure 2).

This disruption impairs the mitochondrial electron transport chain, promoting intracellular reactive oxygen species (ROS) accumulation and oxidative stress in malignant cells (Sharifi-Rad et al., 2018). Increased oxidative stress alters the Bax/Bcl-2 expression ratio, facilitating outer mitochondrial membrane permeabilization and the cytosolic release of cytochrome c and Smac/DIABLO (Figure 2). Once in the cytosol, these factors neutralize inhibitor of apoptosis

proteins (IAPs) and activate the caspase-9/caspase-3 proteolytic cascade, leading to poly(ADP-ribose) polymerase (PARP) cleavage and nuclear DNA fragmentation (Sharifi-Rad et al., 2018; Khan et al., 2017). Furthermore, carvacrol-induced mitochondrial impairment activates endoplasmic reticulum (ER) stress pathways and disrupts intracellular calcium homeostasis, contributing to the suppression of tumor cell survival (Besli et al., 2026).

### ***3.1.3. Quercetin: Modulation of Prosurvival Kinases and Cell Cycle Arrest***

Quercetin, a polyphenolic flavonoid abundant in onions, apples, and berries, inhibits tumor growth by targeting prosurvival kinase cascades and restoring cell cycle checkpoints (Tang et al., 2020; Reyes-Farias & Carrasco-Pozo, 2019). A central mechanism of quercetin-induced cytotoxicity is the suppression of the phosphoinositide 3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) axis (Figure 2). By inhibiting Akt phosphorylation, quercetin blocks the inactivation of pro-apoptotic Bad and glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ), enabling Bad translocation to the mitochondria to promote apoptotic death (Russo et al., 2012; Tang et al., 2020).

Concurrently, quercetin downregulates the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling pathway, resulting in decreased expression of anti-apoptotic proteins such as Mcl-1 and survivin (Reyes-Farias & Carrasco-Pozo, 2019). In cells with wild-type p53 status, quercetin activates the p53 tumor suppressor pathway, inducing transcriptional upregulation of p21/WAF1. This leads to cell cycle arrest at the G2/M phase and directs damaged cells toward programmed apoptotic cell death (Figure 2). Through these combined kinase-inhibitory and cell cycle-regulatory mechanisms, quercetin sensitizes malignant cells to apoptotic elimination (Tang et al., 2020; Reyes-Farias & Carrasco-Pozo, 2019).

### ***3.1.4. Apigenin: Activation of Death Receptors and Caspase Cascades***

Apigenin, a natural trihydroxyflavone present in parsley, celery, and chamomile, induces programmed cell death in hematologic and solid malignancies by activating both extrinsic and intrinsic apoptotic pathways (Imran et al., 2020; Pan et al., 2021). The primary mechanism involves upregulating cell-surface death receptors, including tumor necrosis factor receptor 1 (TNFR1), Fas (CD95), and death receptors 4/5 (DR4/DR5). This leads to the recruitment of Fas-associated death domain (FADD) and the activation of initiator caspase-8 (Figure 2).

Concurrently, apigenin activates the intrinsic mitochondrial pathway by altering the Bax/Bcl-2 expression ratio, causing mitochondrial membrane potential loss and downstream activation of initiator caspase-9 (Sung et al., 2016). These extrinsic and intrinsic cascades converge at the activation of executioner caspases-3 and -7. Activated caspase-3 cleaves poly(ADP-ribose) polymerase (PARP), impairing cellular DNA repair mechanisms and inducing nuclear DNA fragmentation (Figure 2). Through this multi-caspase activation, apigenin suppresses tumor cell survival and promotes apoptotic death across resistant cancer cells (Imran et al., 2020; Pan et al., 2021).

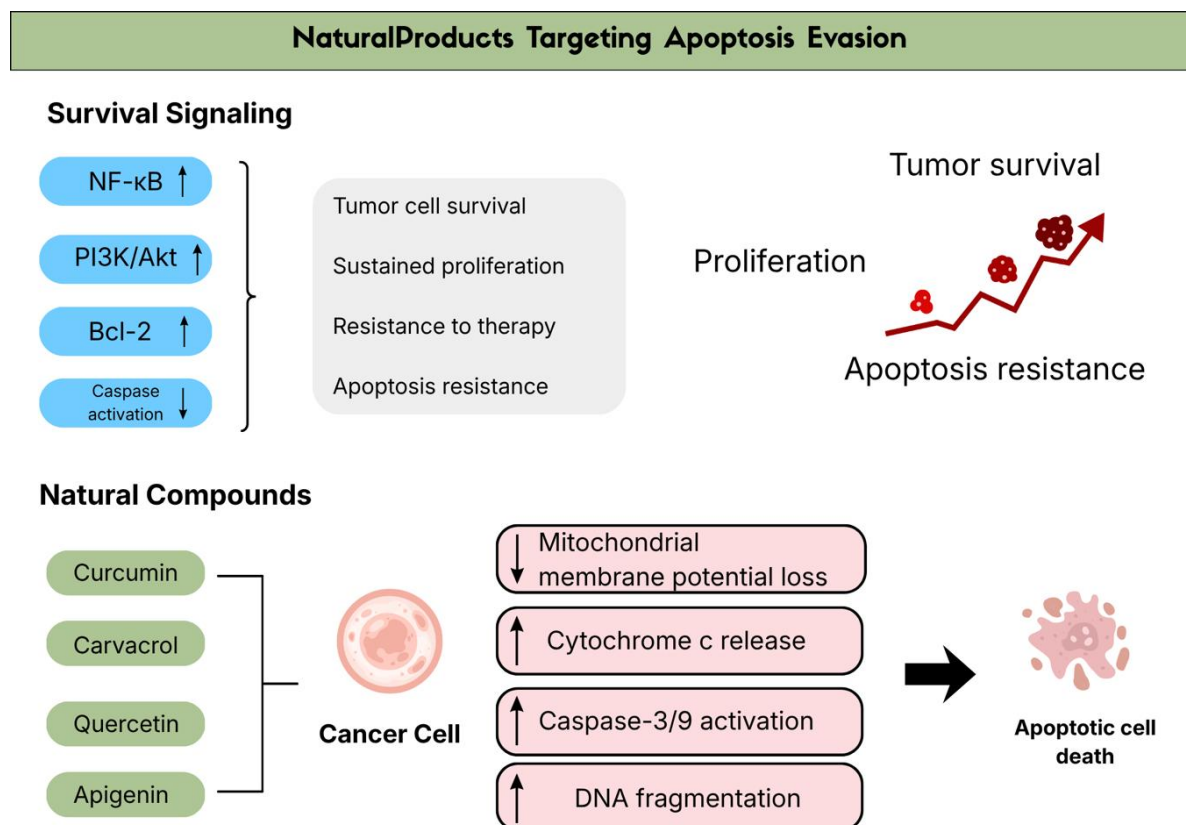


**Figure 2** Schematic representation of apoptosis evasion mechanisms via survival signaling and their reversal by natural compounds.

### 3.2. EMT and the Metastatic Cascade in Cancer Progression

The metastatic cascade remains the primary cause of cancer-related mortality, converting localized primary tumors into systemic disease (Pastushenko & Blanpain, 2019; Welch & Hurst, 2019). This process involves a series of sequential steps: local tissue invasion, intravasation into the blood or lymphatic circulation, survival within the bloodstream, extravasation into distant tissues, and subsequent metastatic colonization (Pastushenko & Blanpain, 2019; Welch & Hurst, 2019).

A critical biological driver of tumor invasion and motility is epithelial–mesenchymal transition (EMT), a cellular reprogramming process in which polarized epithelial cells lose cell–cell adhesion junctions and acquire a migratory, invasive mesenchymal phenotype (Dongre & Weinberg, 2019). At the molecular level, EMT is characterized by the loss of epithelial markers, primarily E-cadherin (encoded by CDH1) and the concurrent upregulation of mesenchymal markers, including N-cadherin, vimentin, and extracellular matrix-degrading matrix metalloproteinases (MMP-2 and MMP-9) (Pastushenko & Blanpain, 2019; Georgescu et al., 2020).

This phenotypic transition is governed by a conserved network of core EMT-inducing transcription factors, including Snail, Slug, Twist, and ZEB1/2, alongside key oncogenic signaling pathways such as Transforming Growth Factor-beta (TGF-beta), Wnt-beta-catenin, and STAT3 (Dongre & Weinberg, 2019; Georgescu et al., 2020). Inhibiting the EMT transcriptional program and suppressing invasive signaling cascades prior to distant colonization represents an important therapeutic axis in preventing metastatic progression.

### ***3.2.1. Resveratrol: Suppression of Extracellular Matrix Remodeling and Invasion***

Resveratrol, a polyphenolic stilbenoid present in grapes, berries, and *Polygonum cuspidatum*, inhibits metastatic progression by modulating extracellular matrix (ECM) degradation and epithelial–mesenchymal transition (EMT) signaling (Ren et al., 2021; Batirel et al., 2025). A principal mechanism of resveratrol-mediated anti-metastatic activity is the downregulation of matrix metalloproteinases, specifically MMP-2 and MMP-9 (Figure 3). By suppressing MMP expression and enzymatic activity, resveratrol reduces extracellular matrix proteolysis, thereby limiting tumor cell invasion into adjacent tissues and vascular structures (Ren et al., 2021).

In addition to enzymatic suppression, resveratrol inhibits key signaling pathways that drive EMT, including Transforming Growth Factor-beta (TGF-beta) and Wnt-beta-catenin networks (Figure 3). Inhibition of these cascades prevents the nuclear translocation and accumulation of beta-catenin, leads to the upregulation of membrane-bound E-cadherin, and represses mesenchymal markers such as N-cadherin and vimentin (Song et al., 2019). Through the dual regulation of ECM-degrading enzymes and EMT-inducing transcription factors, resveratrol attenuates cellular migration, invasion, and distant metastatic dissemination (Batirel et al., 2025).

### ***3.2.2. Luteolin: Transcriptional Regulation of EMT Drivers and Cadherin Expression***

Luteolin, a polyphenolic flavone found in celery, parsley, and chamomile, represses the epithelial–mesenchymal transition (EMT) program in cancer cells by targeting upstream kinase networks and EMT-inducing transcription factors (Qin et al., 2021; Imran et al., 2019). Mechanistically, luteolin inhibits the Mitogen-Activated Protein Kinase (MAPK/ERK) and Phosphoinositide 3-kinase (PI3K/Akt) signaling pathways, resulting in the transcriptional downregulation of primary EMT drivers, specifically Snail and Twist (Figure 3).

By suppressing Snail and Twist expression, luteolin relieves transcriptional repression at the CDH1 promoter, restoring membrane-bound E-cadherin levels (Figure 3). This upregulation of E-cadherin stabilizes cell–cell adhesion, reduces vimentin expression, and blocks the transition of tumor cells toward a migratory, mesenchymal phenotype (Qin et al., 2021; Pan et al., 2022). Consequently, luteolin impairs tumor cell motility, matrix invasion, and metastatic dissemination across human cancer models (Imran et al., 2019; Pan et al., 2022).

### ***3.2.3. Honokiol: Inhibition of Cancer Stemness and Self-Renewal Signaling***

Honokiol, a natural biphenolic neolignan isolated from the bark of *Magnolia officinalis*, represses cancer stem cell (CSC) phenotypes and self-renewal pathways that drive tumor recurrence, metastasis, and therapeutic resistance (Ong et al., 2020; Avtanski et al., 2014). Cancer stem cells represent a subpopulation within tumors possessing embryonic self-renewal properties and high invasive capacity. Mechanistically, honokiol suppresses core embryonic transcription factors, including Oct4, Sox2, and Nanog, that maintain the CSC stemness state (Figure 3).

This transcriptional suppression is mediated by the inhibition of constitutively active self-renewal cascades, particularly Signal Transducer and Activator of Transcription 3 (STAT3) and Sonic Hedgehog (Shh) signaling pathways (Figure 3). By disrupting these signaling networks, honokiol reduces the side population fraction, impairs mammosphere and tumorsphere formation in vitro, and sensitizes chemoresistant cell lines to conventional therapeutics (Ong et

al., 2020). Through the targeted suppression of CSC self-renewal and stemness drivers, honokiol attenuates metastatic colonization and tumor persistence (Avtanski et al., 2014).

### 3.2.4. Berberine: Attenuation of Cellular Migration and Invasive Capacity

Berberine, an isoquinoline alkaloid isolated from *Berberis* species, suppresses tumor cell migration and metastatic colonization by targeting EMT-associated signaling cascades and matrix degradation (Rauf et al., 2021; Samadi et al., 2020). Berberine inhibits AMPK-mediated pathways and represses key transcription factors regulating EMT, resulting in reduced vimentin expression and restoration of E-cadherin levels (Figure 3). Furthermore, berberine downregulates MMP-2 and MMP-9 activity, impairing matrix degradation and vascular intravasation (Rauf et al., 2021). Through these actions, berberine suppresses distant metastatic organ colonization across solid tumor models (Samadi et al., 2020).

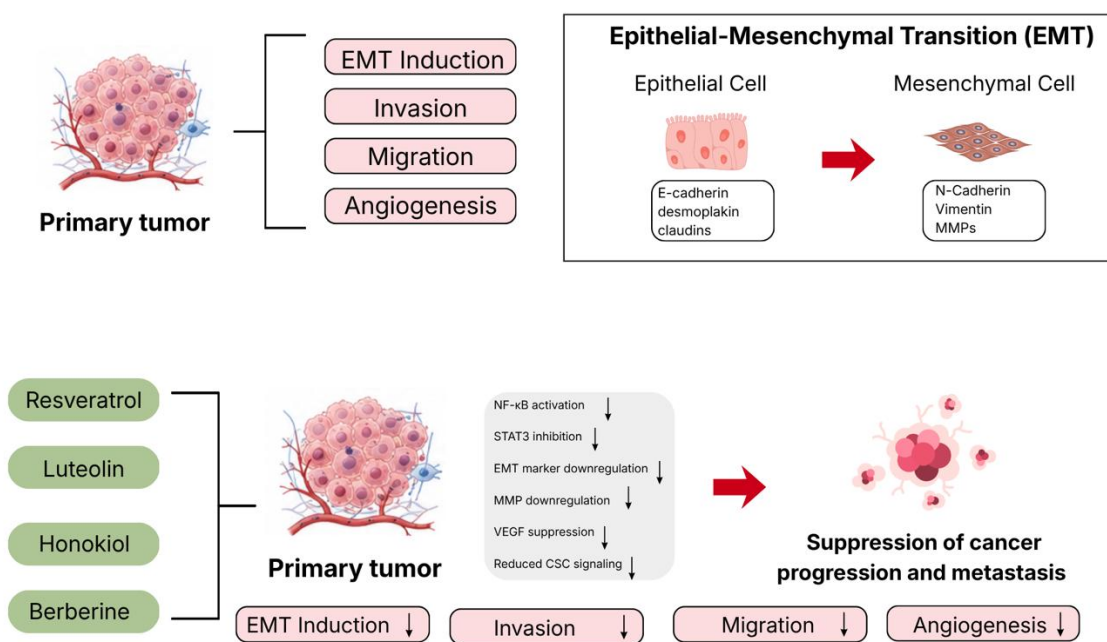


**Figure 3** Schematic illustration of the epithelial-mesenchymal transition (EMT) in primary tumors and its suppression by natural plant products.

### 3.3. The Role of Oxidative Stress and Redox Imbalance in Malignancy

Oxidative stress, defined as an imbalance between reactive oxygen species (ROS) production and cellular antioxidant defense capacity, regulates both tumorigenesis and cancer progression (Hayes et al., 2020). Under physiological conditions, regulated ROS levels act as second messengers in cell proliferation and signaling. However, in malignant cells, metabolic rewiring, mitochondrial dysfunction, and chronic inflammatory cues cause a persistent elevation of intracellular ROS (Negri et al., 2018).

This sustained oxidative environment promotes genomic instability, induces DNA damage, and leads to the constitutive activation of oncogenic transcription factors, particularly Nuclear Factor-kappa B (NF-κB) and Hypoxia-Inducible Factor-1 alpha (HIF-1α) (Figure 4). Furthermore, chronic oxidative stress remodels the tumor microenvironment by activating tumor-associated fibroblasts, driving extracellular matrix remodeling, and stimulating Vascular

Endothelial Growth Factor (VEGF)-mediated angiogenesis (Figure 4). Consequently, modulating cellular redox homeostasis and targeting microenvironmental survival signaling represent key approaches to suppressing tumor adaptation and progression (Negri et al., 2018; Hayes et al., 2020).

### ***3.3.1. Epigallocatechin Gallate (EGCG): Tumor Redox Regulation and Pro-Oxidant Effects***

Epigallocatechin gallate (EGCG), the primary polyphenolic catechin isolated from green tea (*Camellia sinensis*), regulates cellular redox balance and ROS-dependent signaling cascades in human malignancies (Khan & Mukhtar, 2019; Negri et al., 2018). EGCG exhibits cell type-dependent dual redox activities. In non-transformed physiological tissues, EGCG functions as an antioxidant free radical scavenger that upregulates cytoprotective enzymes to limit oxidative DNA damage. Conversely, within the altered metabolic environment of cancer cells, EGCG exerts pro-oxidant actions, promoting intracellular ROS accumulation (Figure 4).

This targeted ROS elevation leads to mitochondrial outer membrane permeabilization, cytochrome c release, and induction of intrinsic apoptosis (Li et al., 2024; Negri et al., 2018). Concurrently, EGCG suppresses constitutively active Nuclear Factor-kappa B (NF- $\kappa$ B) and Hypoxia-Inducible Factor-1  $\alpha$  transcriptional networks (Figure 4). Through the inhibition of these factors, EGCG downregulates downstream matrix metalloproteinases (MMP-2 and MMP-9) and Vascular Endothelial Growth Factor (VEGF), suppressing tumor invasion, extracellular matrix remodeling, and angiogenic sprouting within the tumor microenvironment (Khan & Mukhtar, 2019; Negri et al., 2018).

### ***3.3.2. Propolis: Neutralization of Inflammatory Signaling and Angiogenic Factors***

Propolis, a complex resinous mixture produced by honeybees (*Apis mellifera*) from diverse botanical origins, modulates tumor–microenvironment interactions through its high concentration of polyphenols, flavonoids, and phenolic esters (Sforcin, 2016; Li et al., 2021). As a multi-component natural product, propolis targets parallel signaling nodes within the tumor microenvironment. At the cellular level, propolis attenuates chronic inflammatory signaling by downregulating Interleukin-6 (IL-6), Signal Transducer and Activator of Transcription 3 (STAT3), and Nuclear Factor-kappa B (NF- $\kappa$ B) activation, thereby suppressing inflammation-driven tumor progression (Figure 4) (Li et al., 2021; Zhu et al., 2024).

Simultaneously, propolis targets tumor vascularization by suppressing Vascular Endothelial Growth Factor (VEGF) expression and secretion (Figure 4) (Sforcin, 2016; Zhu et al., 2024). Inhibition of VEGF signaling reduces endothelial cell proliferation, migration, and capillary tube formation, limiting nutrient supply to the primary tumor mass. Through these combined anti-inflammatory and anti-angiogenic actions, propolis disrupts supportive stromal signaling and impairs tumor adaptation (Li et al., 2021; Zhu et al., 2024).

### ***3.3.3. Sulforaphane: Activation of Nrf2-Mediated Cytoprotective Responses***

Sulforaphane, an organosulfur isothiocyanate abundant in cruciferous vegetables such as broccoli and Brussels sprouts, regulates cytoprotective signaling and cellular detoxification networks in human malignancies (Mangla et al., 2020). The primary mechanism of action involves the activation of the Nuclear Factor Erythroid 2–Related Factor 2 (Nrf2) signaling pathway, a central regulator of the cellular antioxidant response (Figure 4).

Mechanistically, sulforaphane reacts with specific cysteine residues on Kelch-like ECH-associated protein 1 (Keap1), inducing a conformational change that disrupts the Keap1–Nrf2 interaction (Figure 4). This allows stabilization and nuclear translocation of Nrf2, where it heterodimerizes with Small Maf proteins and binds to Antioxidant Response Elements (ARE) in target gene promoters (Su et al., 2018; Mangla et al., 2020). This transcriptional binding induces Phase II detoxification enzymes including heme oxygenase-1 (HO-1), NAD(P)H:quinone oxidoreductase 1 (NQO1), and glutathione S-transferases (GSTs) which neutralize reactive oxygen species (ROS) and electrophiles (Figure 4).

Through Nrf2 pathway activation, sulforaphane reduces oxidative DNA damage in non-transformed cells while selectively triggering cell cycle arrest and intrinsic apoptosis in malignant phenotypes (Su et al., 2018; Mangla et al., 2020).

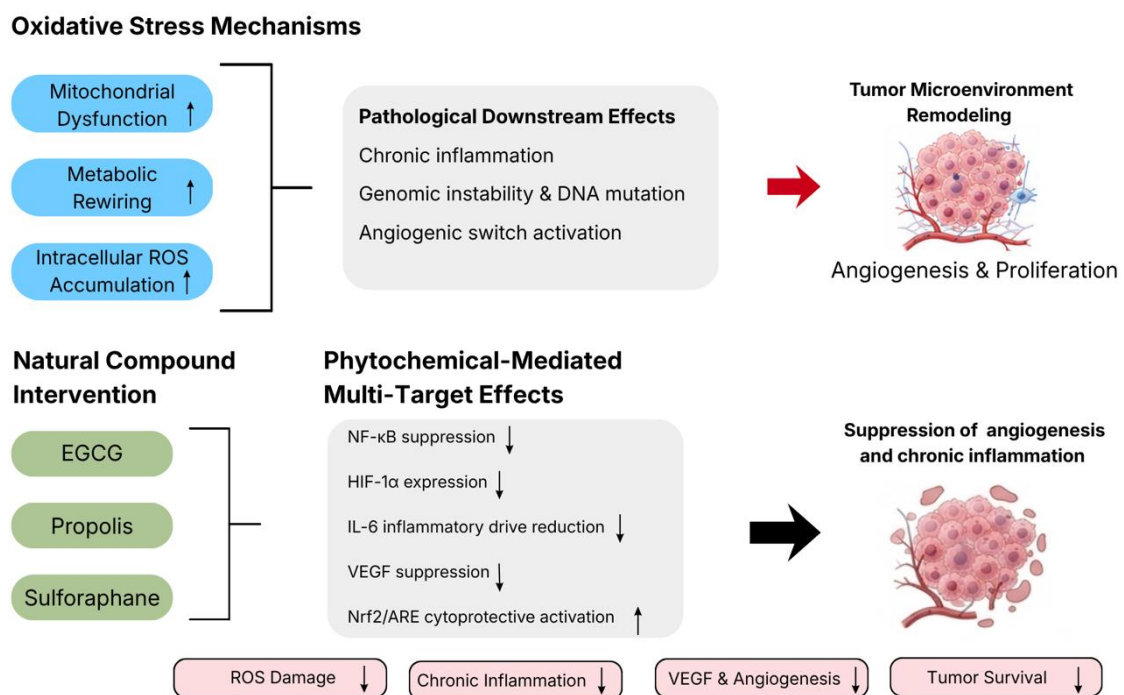


**Figure 4** Schematic representation of oxidative stress and tumor microenvironment remodeling in cancer progression and their targeted modulation by EGCG, propolis, and sulforaphane

#### 4. Challenges and Limitations of Natural Products in Cancer Therapy

Despite preclinical efficacy observed across in vitro and in vivo models, several pharmacological and biopharmaceutical limitations obstruct the clinical translation of plant-derived bioactive agents (Tomeh et al., 2019; Atanasov et al., 2021). Phytochemicals including curcumin, resveratrol, and quercetin exhibit poor systemic bioavailability, primarily restricted by low aqueous solubility, extensive first-pass hepatic metabolism (via rapid glucuronidation and sulfation), and rapid systemic clearance (Tomeh et al., 2019; Del Rio et al., 2013). Consequently, achieving therapeutic concentrations within target tumor tissues remains a major barrier using unformulated administration routes. Although numerous in vitro models demonstrate potent multi-targeted regulations, such as the inhibition of IKK-mediated NF-κB activation and blockade of nuclear translocation, translating these specific mechanisms into human systems requires overcoming these pharmacokinetic barriers.

In addition, tumor heterogeneity and potential herb–drug interactions complicate the clinical pharmacokinetics of natural compounds. Select phytochemicals modulate cytochrome P450 (CYP450) enzyme isoforms and drug efflux transporters (such as P-glycoprotein), potentially altering the clearance and systemic exposure of co-administered chemotherapeutic agents (Atanasov et al., 2021; Yeung et al., 2018).

A further challenge involves transitioning natural products from crude nutraceuticals to pharmaceutical-grade therapeutics. Although multi-component matrices such as propolis are widely consumed as functional foods, clinical implementation demands rigorous chemical standardization, batch-to-batch reproducibility, identification of primary active constituents, and validated dose–response relationships (Sforcin, 2016; Atanasov et al., 2021). Chemical variability driven by geographical origin and extraction methodologies presents regulatory hurdles regarding quality control and safety profiling, necessitating standardized nano-formulation approaches (e.g., micelles, liposomes, and polymeric nanoparticles) to protect these compounds from premature degradation and to establish safe therapeutic windows in ongoing Phase I and II clinical trials (Sforcin, 2016; Tomeh et al., 2019).

## **5. Future Perspectives**

The translational viability of natural products in oncology depends on addressing their inherent biopharmaceutical and pharmacological limitations. Transitioning plant-derived bioactive agents from experimental settings toward clinical evaluation requires multidisciplinary approaches that integrate materials science, medicinal chemistry, and computational biology. Advanced delivery platforms, such as polymeric nanoparticles, liposomes, and nanomicelles, are being investigated to address low aqueous solubility, rapid metabolic clearance, and limited tumor tissue targetability observed in compounds like curcumin, resveratrol, and quercetin. In parallel, targeted medicinal chemistry approaches, including semi-synthetic modifications and structure–activity relationship optimization, offer opportunities to improve the pharmacodynamics, metabolic stability, and target selectivity of molecules such as carvacrol, apigenin, and honokiol. Furthermore, the integration of artificial intelligence, machine learning algorithms, and multi-omics profiling with network pharmacology facilitates the systematic analysis of multi-target natural products, aiding in candidate selection and the design of potential combination strategies with standard chemotherapeutics or immunotherapies. Combining nano-formulation approaches, structural optimization, and computational target identification may enhance the translational feasibility and therapeutic potential of natural bioactive compounds in cancer management.

## **6. Conclusion**

The rising global burden and structural heterogeneity of cancer highlight the clinical need for multi-target therapeutic strategies capable of modulating complex biological networks. Evasion of apoptosis, metastatic dissemination, and microenvironmental redox alterations represent interconnected mechanisms that contribute to tumor resistance against conventional single-target therapies. As reviewed, plant-derived bioactive compounds and complex natural matrices provide a polypharmacological framework for targeting these survival cascades at multiple regulatory checkpoints.

Specifically, compounds such as curcumin, carvacrol, quercetin, and apigenin promote apoptotic susceptibility by modulating Bcl-2 family expression and triggering caspase-dependent proteolysis. Concurrently, agents including resveratrol, luteolin, and honokiol attenuate invasive and metastatic potential by repressing epithelial-mesenchymal transition (EMT) transcription factors and cancer stemness pathways. Furthermore, EGCG, sulforaphane, and multi-component matrices such as propolis regulate tumor microenvironment dynamics and cellular redox homeostasis by suppressing pro-inflammatory signaling and modulating cytoprotective responses. Although biopharmaceutical limitations regarding oral bioavailability, metabolic stability, and pharmaceutical standardization remain to be addressed through advanced nano-delivery systems and structural optimization, these natural agents present a valuable framework for contemporary oncological research. Driven by expanding research efforts and translational studies, these bioactive scaffolds continue to gain significance in modern oncology underscoring that comprehensive, multi-targeted paradigms in future cancer therapy will increasingly rely on the strategic integration of these versatile natural molecules.

## **Declarations**

### ***Ethics Statement***

Research and publication ethics were strictly observed throughout the preparation of this manuscript. As this work is a literature-based review and did not involve human participants, animal experimentation, or biological tissue samples, formal ethical committee approval was not required.

### ***Conflict of Interest***

The author declares no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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### ***Use of Artificial Intelligence***

The author used AI-assisted tools for language editing, translation and reference formatting checks. All scientific content, analytic decisions, interpretations, and final wording were determined and verified by the author, who takes full responsibility for every claim in the manuscript.

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REVIEW ARTICLE

## Hydroxyapatite-Based Targeted Drug Delivery Systems for HER2-Positive Breast Cancer: The Role of Trastuzumab and Folic Acid Functionalization

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### ABSTRACT

Worldwide, breast cancer continues to be one of the most frequently diagnosed malignancies and continues to pose a significant challenge in cancer therapy. Despite the significant improvement in patient survival that HER2-targeted therapies, such as trastuzumab, have achieved, their therapeutic efficacy remains restricted by challenges such as cardiotoxicity, acquired resistance, limited tumor accumulation, and off-target effects. Recent developments in drug delivery systems have concentrated on the enhancement of treatment outcomes by utilizing targeted delivery strategies and controlled drug release. Among various carrier materials, hydroxyapatite (HAp) has attracted considerable attention due to its excellent biocompatibility, bioactivity, porous structure, high drug-loading capacity, and ease of surface functionalization. These characteristics make HAp a promising candidate for the development of advanced drug delivery platforms capable of enhancing therapeutic efficiency while minimizing systemic side effects. Furthermore, surface modification with targeting ligands such as folic acid offers additional opportunities for improving local cellular recognition and targeted drug delivery. This review summarizes current developments in hydroxyapatite-based drug delivery systems for breast cancer therapy, with particular emphasis on trastuzumab delivery, folic acid-mediated targeting approaches, and hydroxyapatite microsphere technologies. Recent studies investigating HAp-based carriers, targeted delivery systems, and multifunctional therapeutic platforms are discussed, together with their advantages, limitations, and clinical potential. In addition, the role of microsphere-based delivery systems in achieving sustained drug release and enhanced therapeutic performance is highlighted. Current literature demonstrates the potential of hydroxyapatite carriers for the delivery of various therapeutic agents; however, studies integrating trastuzumab delivery, folic acid-mediated targeting, and hydroxyapatite microspheres within a single platform remain limited. This gap highlights the need for multifunctional carrier systems capable of combining controlled release with selective cellular recognition and targeted delivery. The available literature suggests that hydroxyapatite microspheres may provide a versatile platform for HER2-targeted therapy, with trastuzumab potentially incorporated as a therapeutic cargo or used as a surface-bound targeting ligand. These approaches differ in their intended functions and may enable controlled drug release and HER2-mediated targeting, respectively.

**Keywords:** *Hydroxyapatite; microspheres; drug delivery system; HER2-positive breast cancer*

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## 1. Introduction

Breast cancer is still one of the most common malignancies and a leading cause of cancer-related mortality among women worldwide. According to global cancer statistics, breast cancer accounted for approximately 2.3 million new cases in 2022, representing one of the most frequently diagnosed cancers among women. Breast cancer remains associated with substantial morbidity and mortality, despite significant progress in early diagnosis and therapeutic strategies (Bray et al., 2024). Breast cancer is a heterogeneous disease consisting of multiple molecular subtypes with biological characteristics and clinical outcomes. Among these subtypes, human epidermal growth factor receptor 2 (HER2)-positive breast cancer is characterized by amplification and/or overexpression of HER2. Breast cancers with HER2 overexpression and/or amplification account for approximately 15–20% of cases and constitute a highly aggressive subtype (Pupa et al., 2021).

Current treatment approaches for breast cancer include surgery, radiotherapy, chemotherapy, endocrine therapy, immunotherapy, and targeted therapies. The selection of treatment strategies depends on tumor subtype, disease stage, receptor expression profile, and patient-specific factors (Waks & Winer, 2019). Although these therapeutic modalities have significantly improved patient survival, many conventional treatments may be associated with off-target exposure and treatment-related toxicity. For example, trastuzumab treatment is associated with cardiac toxicity, highlighting the need to consider treatment-related adverse effects in HER2-targeted therapy (Early Breast Cancer Trialists' Collaborative Group, 2021).

As a result of the development of HER2-targeted therapies, clinical outcomes for HER2-positive breast cancer have improved significantly. Nowadays, the most successful of these targeted therapies is trastuzumab, a monoclonal antibody that specifically targets HER2 receptors. However, trastuzumab treatment may be associated with cardiotoxicity, which remains an important challenge in its clinical use (Early Breast Cancer Trialists' Collaborative Group, 2021; Gu et al., 2024). These challenges have led to research into developing new drug delivery systems aimed at minimizing systemic side effects and enhancing therapeutic effects.

Among the various carrier systems investigated for cancer therapy, hydroxyapatite (HAp)-based microspheres have attracted considerable interest because of their biocompatibility, bioactivity, porous structure, and potential for drug loading and surface functionalization (Hou et al., 2022; H. Huang et al., 2020). In parallel, active targeting strategies using ligands such as folic acid (FA) have been explored in cancer drug delivery systems to enhance receptor-mediated cellular recognition and targeting selectivity (Sudimack & Lee, 2000). This review summarizes current literature on hydroxyapatite-based drug delivery systems for breast cancer therapy, with particular emphasis on microsphere formulations, folic acid-mediated targeting, and the feasibility of trastuzumab incorporation or surface conjugation for HER2-directed treatment. Current evidence, technological limitations, and key translational challenges are also discussed to identify priorities for future research.

### 1.1 Scope and Literature Search Strategy

A literature search was conducted to identify relevant studies published between 2000 and 2025 on hydroxyapatite-based drug delivery systems, hydroxyapatite microspheres, breast cancer, HER2-targeted therapy, trastuzumab, folic acid-mediated targeting, and related therapeutic

strategies. An extensive literature search was conducted in PubMed, Scopus, and Google Scholar databases to evaluate the current developments in hydroxyapatite-based drug delivery systems for HER2-positive breast cancer. The literature review was conducted with a particular focus on specific research areas, using the primary keywords “hydroxyapatite,” “hydroxyapatite microspheres,” “breast cancer,” “HER2,” “trastuzumab,” “folic acid,” “targeted drug delivery,” and “controlled drug release.” Inclusion criteria excluded pill carriers and decontextualized conference abstracts among these publications, as well as studies unrelated to drug delivery or targeted therapy. In addition to these reviews, about 200 or more records were scanned to define the boundaries, and 70 representative and peer-reviewed studies were selected.

## **2. HER2-Positive Breast Cancer and Targeted Therapies**

HER2 belongs to the ErbB family of receptor tyrosine kinases and plays a crucial role in regulating cell proliferation, differentiation, migration, and survival. Amplification of the HER2 gene results in excessive receptor expression, leading to continuous activation of downstream signaling pathways such as PI3K/Akt and MAPK, ultimately promoting tumor progression and metastasis. The emergence of HER2-targeted therapeutics has completely transformed the management of this disease subtype. Trastuzumab is a humanized monoclonal antibody that selectively binds to the extracellular domain of HER2 receptors. Through receptor blockade, trastuzumab inhibits HER2-mediated signaling pathways, induces antibody-dependent cellular cytotoxicity (ADCC), and suppresses tumor growth (Nami et al., 2018). When trastuzumab is immobilized on the surface of a carrier like HAp, it's important to maintain the antibody's orientation and biological activity. Random adsorption or non-specific covalent binding can cause antibodies to have heterogeneous orientations, which can reduce accessibility of the Fab regions that recognize the antigen and affect HER2 recognition. Also, trastuzumab-mediated ADCC involves the interaction of the antibody's Fc region with Fc $\gamma$  receptors on immune effector cells, especially natural killer cells, so the immobilization strategy needs to preserve the Fc region's accessibility and functional integrity (Collins et al., 2012; Wong & Lee, 2012). Directed immobilization strategies may help reduce steric hindrance and keep the antibody's binding sites accessible. In this context, Fc-directed conjugation, affinity-based immobilization, or linker-mediated attachment can be considered potential approaches for controlling the orientation of antibodies on the carrier surface (Nieto et al., 2020; Selepe et al., 2024). Additionally, it has been experimentally shown that proteins can be immobilized in a directed manner on HAp surfaces using bifunctional bisphosphonate linkers, which supports the feasibility of controlled presentation of proteins on HAp surfaces (Yewle et al., 2012). Nevertheless, whether surface-immobilized trastuzumab retains its HER2-binding and Fc-mediated effector functions after conjugation to HAp requires experimental validation.

In addition to trastuzumab, several HER2-targeted agents have been developed, including pertuzumab, lapatinib, trastuzumab deruxtecan, and ado-trastuzumab emtansine (T-DM1). These therapies have significantly improved progression-free survival and overall survival in HER2-positive breast cancer patients (Gu et al., 2024; Zheng et al., 2023). Although antibody-drug conjugates (ADCs) such as trastuzumab deruxtecan and T-DM1 have successfully achieved drug delivery targeting HER2 in clinical practice, HAp-based systems can offer different and potentially complementary delivery approach. Unlike conventional ADCs, HAp

carriers provide a porous matrix that allows the transport of therapeutic agents via encapsulation or surface loading, while also enabling controlled release and additional surface functionalization (De Lama-Odría et al., 2022; Dong et al., 2023). This modular structure may allow the integration of multiple functional components within a single carrier and provide greater flexibility in regulating drug loading and release characteristics. Therefore, HAp-based platforms should be considered as an alternative and potentially complementary strategy to established HER2-targeted therapies rather than as a replacement for clinically approved ADCs.

Despite these advances, several limitations remain. One of the major concerns associated with trastuzumab therapy is cardiotoxicity, which may lead to left ventricular dysfunction and heart failure in susceptible patients. Importantly, trastuzumab-associated cardiotoxicity is considered an on-target effect because HER2/ErB2 signaling also plays a crucial role in cardiomyocytes (Lin et al., 2022). Furthermore, systemic administration often results in suboptimal drug accumulation at tumor sites and may contribute to the emergence of acquired therapeutic resistance (Moo et al., 2018). To address these challenges, considerable efforts have focused on the development of advanced delivery platforms capable of enhancing trastuzumab stability, controlling drug release, improving local drug availability, and reducing systemic toxicity. Nanoparticles, liposomes, polymeric carriers, hydrogels, and microsphere-based systems have all demonstrated promising potential for improving the therapeutic performance of HER2-targeted agents (Truffi et al., 2018; Vanni et al., 2025). Recent studies have shown that surface-functionalized delivery systems decorated with antibodies or targeting ligands can improve cellular uptake and enhance therapeutic efficacy. Such approaches may provide more effective treatment strategies for HER2-positive breast cancer while minimizing adverse effects associated with conventional systemic administration (Sakhi et al., 2022; Truffi et al., 2018).

### **3. Drug Delivery Systems in Breast Cancer**

Drug delivery systems (DDSs) have emerged as an essential strategy to improve the therapeutic efficacy and safety of anticancer agents. DDSs can improve therapeutic efficacy while reducing systemic toxicity by enabling controlled and sustained drug release, enhancing drug stability, and, depending on the carrier and administration strategy, improving drug distribution and local drug availability. Conventional chemotherapy, in contrast, often suffers from nonspecific biodistribution, rapid systemic clearance, dose-limiting adverse effects, and the development of multidrug resistance. Therefore, extensive research has been performed on the design of advanced delivery platforms to improve the pharmacokinetic and pharmacodynamic profiles of anticancer therapeutics (Peiris et al., 2014; Yao et al., 2020).

The drug delivery strategies can be classified as passive and active targeting approaches in a broad sense. Passive targeting mainly utilizes the enhanced permeability and retention (EPR) effect, while active targeting utilizes ligand-receptor interactions to increase selective cellular recognition and uptake. However, the EPR effect should not be considered a uniform or universally effective mechanism for tumor targeting. The extent of the EPR effect can vary depending on the tumor type and the heterogeneous tumor microenvironment. In addition, the presence and extent of the EPR effect are still debated, and the differences between preclinical models and human tumors may hinder the translation of passive targeting strategies based on the EPR effect into clinical practice (Shi et al., 2020). Among the different targeting ligands

explored, folic acid (FA) has been of particular interest since folate receptors are expressed in various tumors and can serve as attractive targets for tumor-specific drug delivery (Sudimack & Lee, 2000). Some of the carrier platforms investigated for breast cancer treatment include liposomes, polymeric nanoparticles, micelles, hydrogels, inorganic nanoparticles and microspheres (Zhai et al., 2024). Among them, microsphere-based systems have attracted increasing attention due to their high drug loading capacity, protection of encapsulated therapeutics, prolonged drug release and the possibility of surface functionalization (X. Li et al., 2024).

For drug delivery applications in breast cancer, polymeric microspheres made from biodegradable materials such as poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), and their copolymers have been extensively studied. Natural polymers, including chitosan, gelatin, alginate, hyaluronic acid, and silk fibroin have also attracted considerable interest because of their favorable biocompatibility and tunable physicochemical properties (Cai et al., 2024; Zhai et al., 2024). These materials provide versatile delivery platforms because their degradation behavior, mechanical properties, and surface chemistry can be readily tailored to specific therapeutic requirements. However, their widespread clinical translation is still impeded by a variety of obstacles, such as the limited stability of certain therapeutic agents, the complexity of manufacturing, and the difficulties associated with large-scale production (X. Li et al., 2024; Wu et al., 2024). Most recently, hydroxyapatite (HAp)-based microspheres have attracted increasing attention as a promising alternative owing to their biomimetic composition, porous structure, excellent biocompatibility and versatile surface chemistry. These properties enable efficient drug loading while providing opportunities for controlled drug release and further functionalization with targeting ligands, while their potential for targeted drug delivery remains under investigation (Mondal et al., 2018; Qian et al., 2023).

#### 4. Hydroxyapatite as a Drug Carrier

HAp, with the chemical formula  $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ , is a calcium phosphate ceramic and is a principal inorganic component of human dental and bone tissue (Fiume et al., 2021). HAp has been extensively investigated for numerous biomedical applications, including bone regeneration, tissue engineering and drug delivery owing to its chemical similarity to native mineralized tissue. In addition to its established role as a bone substitute, there has been a growing interest in its potential as a multifunctional drug carrier due to its versatile surface chemistry and tunable physicochemical properties (Fiume et al., 2021; Hou et al., 2022).

HAp has some unique advantages as a drug carrier because of its porous structure, high specific surface area, and chemically active surface. These properties permit the efficient loading of various therapeutic agents such as small molecule drugs, peptides, proteins, and nucleic acids. In addition, the presence of calcium and phosphate groups offers active sites for drug adsorption and surface functionalization, allowing a wide variety of drug loading strategies (S.-M. Huang et al., 2022; Lara-Ochoa et al., 2021).

The release profile of HAp-based carriers depends on several factors like particle size, porosity, crystallinity, surface chemistry, and drug-carrier interactions (Mondal et al., 2018). The release of therapeutic agents may occur through diffusion, desorption from the surface of the carrier, gradual dissolution of the mineral matrix, or a combination of these mechanisms, depending on

the loading strategy (Mondal et al., 2018; N. Wang et al., 2019). This tunable release behavior can offer sustained therapeutic exposure and potentially reduce the frequency of administration while maintaining effective drug concentrations. These properties are especially advantageous in the setting of anticancer therapy, where sustained drug availability and reduced systemic exposure could enhance therapeutic efficacy and reduce adverse effects (Qian et al., 2023).

In recent years, HAp microspheres have emerged as particularly attractive delivery platforms due to their spherical morphology, porous structure, and favorable biological interactions. Compared with many conventional polymeric carriers, HAp microspheres combine favorable biocompatibility with intrinsic bioactivity and a mineral composition that closely resembles native hard tissues. These properties make HAp-based microspheres promising candidates for drug delivery applications (S. Li et al., 2023).

Several studies have demonstrated the successful incorporation of antimicrobial peptides, and chemotherapeutic agents within HAp microspheres, highlighting their versatility of HAp as carriers for localized and controlled drug delivery (Hong et al., 2021; H. Huang et al., 2020; Wu et al., 2022). These findings highlight the potential of HAp microspheres as multifunctional platforms capable of combining controlled drug release with further surface functionalization (Zhang et al., 2021). However, the effectiveness of such functionalization for active targeting in microscale HAp systems requires further investigation. Consequently, HAp-based delivery systems have become increasingly important in the development of next-generation cancer therapeutics (Qian et al., 2023).

Another potential advantage of HAp-based carriers is their pH-dependent dissolution behavior. HAp may exhibit higher solubility under acidic conditions; this can contribute to pH-dependent drug release and provide an advantage in acidic biological environments such as tumor microenvironment (Feng et al., 2013). In addition to its role as drug carrier, HAp, particularly in nanoparticle form, has also been reported to exhibit intrinsic antitumor activity. It has been shown that HAp nanoparticles cause intracellular  $\text{Ca}^{2+}$  loading in cancer cells, trigger calpain activation, and consequently activate mitochondrial apoptotic pathways (Dong et al., 2023). These findings suggest that HAp may offer an additional therapeutic potential beyond its conventional role as a drug carrier.

## **5. Folic Acid-Mediated Targeting Strategies**

Active targeting is considered one of the most promising approaches for improving the efficacy and specificity of cancer treatment. Unlike passive targeting, which mainly relies on the EPR effect, active targeting employs specific ligands capable of recognizing molecular markers overexpressed on cancer cells (Bi et al., 2016). Among these ligands, folic acid (FA) has attracted considerable attention because as a targeting ligand, and its incorporation onto HAp surfaces has been investigated for developing FA-functionalized HAp systems (Cipreste et al., 2016).

Folate receptors are membrane-bound glycoproteins involved in cellular folate uptake. While their expression is generally low in most healthy tissues, significantly elevated expression levels have been reported in many cancer cells. This differential expression pattern provides an attractive opportunity for selective drug delivery (Sudimack & Lee, 2000; Tagde et al., 2020). FA is a small, inexpensive, non-immunogenic molecule that can be readily conjugated onto

carrier surfaces without significantly altering their physicochemical properties (Sudimack & Lee, 2000).

FA-functionalized drug delivery systems promote receptor-mediated cellular uptake following binding to folate receptors on cancer cells. As a result, therapeutic agents can be delivered preferentially into cancer cells, enhancing intracellular drug delivery and therapeutic efficacy. For instance, folate-functionalized liposomes have demonstrated FR-mediated internalization, enhanced cellular uptake, and improved anticancer activity in FR-overexpressing breast cancer cells (Dinakar et al., 2023).

The incorporation of FA onto HAp carriers represents an especially attractive strategy because it combines the favorable drug-loading characteristics of hydroxyapatite with the potential for folate receptor-mediated cellular recognition and uptake (Cipreste et al., 2016; Verma et al., 2020). However, the therapeutic benefit of FA-mediated targeting is expected to depend on factors such as folate receptor expression and the physicochemical characteristics of the carrier system. Surface functionalization can be achieved through surface chemical modification using linker-mediated strategies like PEG-based functionalization (Qian et al., 2023). Following successful conjugation, FA-modified HAp carriers can enhance interaction with folate receptor-positive tumor cells (Verma et al., 2020).

Recent studies on folate-functionalized drug delivery systems and targeted microspheres suggest that folate-mediated targeting has promising potential for enhancing selective drug delivery and therapeutic performance (Yao et al., 2020; Zha et al., 2022). Consequently, the integration of FA-functionalized HAp microspheres with HER2-targeted therapeutics such as trastuzumab represents a potential design strategy that warrants further experimental and translational investigation.

## **6. Current Studies on Hydroxyapatite Microspheres for Cancer Therapy**

### ***6.1. Hydroxyapatite Microspheres in Drug Delivery Applications***

Hydroxyapatite (HAp) microspheres have been increasingly investigated as versatile platforms for therapeutic drug delivery (Mondal et al., 2018). Their porous structure and tunable physicochemical properties enable efficient drug loading, while their pore structure can influence the kinetics of controlled and sustained drug release (Lai et al., 2016). Over the past decade, HAp microspheres have been investigated for the delivery of proteins and antimicrobial agents, demonstrating their versatility for the controlled delivery of biological molecules (Fu et al., 2011; Soriano-Souza et al., 2015). Furthermore, porous hollow HAp microspheres have demonstrated high drug-loading capacity and pH-responsive sustained-controlled release, highlighting their potential for anticancer drug delivery (Lai et al., 2016).

Previous studies have shown that HAp microspheres can encapsulate both small-molecule therapeutics and biomacromolecules and can maintain controlled release profiles (Fu et al., 2011; S. Wang et al., 2010). Apart from drug delivery, surface functionalization strategies have extended their applications to targeted and other specialized biomedical applications (Zhang et al., 2021).

Because of their micrometer-scale size, hydroxyapatite microspheres are more suitable for implantation for local or regional drug release purposes than systemic intravenous tumor

targeting (Fu et al., 2011; Long et al., 2013). In this approach, drug-loaded microspheres can be placed directly at the resection site after surgical removal of the tumor, ensuring local and long-term drug release. Indeed, local drug release, tumor regrowth, and metastasis development can be monitored following this process. This type of locoregional implantation approach allows the therapeutic agent to be delivered directly to the target site and controlled/sustainable release without requiring the microspheres to be extravasated into the tumor tissue by being delivered into the systemic circulation (Nwazojie et al., 2023). Table 1 presents representative studies in HAp microsphere-based systems for drug delivery.

**Table 1** Representative studies investigating hydroxyapatite microsphere-based drug delivery systems

| Therapeutic agent | Carrier                                   | Size                                                             | Loading strategy                                                                | Model                                                                                   | Major Findings                                                                                                                                                                           | Administration Route                                             | Ref.                    |
|-------------------|-------------------------------------------|------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|-------------------------|
| Tamoxifen         | Porous HAp Microspheres                   | 0.8-2 $\mu\text{m}$                                              | Covalent attachment                                                             | The breast cancer cell line MCF-7                                                       | Sustained tamoxifen release with enhanced cytotoxicity against MCF-7 cells                                                                                                               | Not reported                                                     | (Kırbıyık et al., 2022) |
| Doxorubicin       | Porous HAp/Gelatin Composite Microspheres | 45 $\mu\text{m}$                                                 | Chitosan-assisted bonding (Hydrogen bonding)                                    | Human osteosarcoma-derived G-292 cells                                                  | 99% drug entrapment efficiency with sustained doxorubicin release (45% release over 6 months) while maintaining anticancer activity.                                                     | Not reported                                                     | (Wu et al., 2022)       |
| Paclitaxel (PTX)  | PLGA-PCL microspheres                     | 1.35–5.79 $\mu\text{m}$ (SEM); 6.2–9.2 $\mu\text{m}$ (DLS, DPBS) | Drug encapsulation in PLGA-PCL microspheres                                     | MDA-MB-231 TNBC xenograft in athymic nude mice                                          | Localized and sustained drug release after tumor resection; targeted formulations reduced/prevented local tumor regrowth and showed no detectable lung metastasis in the targeted groups | Locoregional / local implantation at the surgical resection site | (Nwazojie et al., 2023) |
| Ciprofloxacin     | Mesoporous hierarchical HAp Microspheres  | 5 $\mu\text{m}$                                                  | Surface adsorption and pore loading                                             | Not reported                                                                            | 61% drug loading with sustained ciprofloxacin release for 12 days; 79% of ciprofloxacin was released over 300 hours.                                                                     | Not reported                                                     | (Daryan et al., 2025)   |
| Resveratrol (Res) | n-HA/CS composite microspheres            | 30.75–110.87 $\mu\text{m}$ (depends on formulation parameters)   | Encapsulation during microsphere fabrication by emulsion chemical cross-linking | OVX-induced osteoporotic SD rats; femoral bone defect model                             | Enhanced osteogenic differentiation, reduced inflammation, accelerated entochondrosthosis and bone regeneration; improved healing of osteoporotic bone defects                           | Local implantation into femoral bone defect                      | (L. Li et al., 2021)    |
| HHC36 Peptide     | Hierarchical HAp Microspheres             | Not reported                                                     | Surface adsorption via electrostatic interactions                               | Antibacterial activity tested with <i>E. coli</i> and <i>S. aureus</i>                  | Highest peptide loading efficiency and sustained release over 9 days with prolonged antibacterial activity.                                                                              | Not reported                                                     | (Hong et al., 2021)     |
| Gentamicin        | Mesoporous carbonated HAp microspheres    | ~5 $\mu\text{m}$                                                 | Adsorption/soaking                                                              | In vitro testing via <i>S. epidermidis</i> and human bone marrow stromal cells (hBMSCs) | 70–75% drug-loading efficiency; sustained gentamicin release for up to 6 days; reduced bacterial adhesion and biofilm formation; good biocompatibility                                   | Local drug delivery                                              | (Guo et al., 2013)      |

In anticancer studies, HAp microspheres have been increasingly studied as carriers for therapeutic agents. Their porous structure, tunable physicochemical properties, and ability to sustain drug release make them attractive candidates for anticancer drug delivery. These features have led to an increasing interest in the exploration of HAp microspheres for the delivery of chemotherapeutic agents in different cancer models (Saber-Samandari et al., 2016).

The main goal has been to improve drug loading to prolong drug release while maintaining the therapeutic activity of the loaded agents. Examples of interest include the encapsulation of doxorubicin and tamoxifen, which showed sustained drug release and cytotoxic activity in cancer cell models (Kırbıyık et al., 2022; Wu et al., 2022). Representative studies have reported promising results in drug loading and efficiency. Wu et al. developed porous hydroxyapatite-gelatin composite microspheres loaded with doxorubicin and reported sustained release behavior together with enhanced drug loading efficiency. The incorporation of chitosan further improved release control and carrier stability (Wu et al., 2022).

Similarly, Kırbıyık et al. investigated tamoxifen-loaded hydroxyapatite microspheres for breast cancer treatment. Their findings demonstrated that HAp microspheres could effectively deliver tamoxifen to MCF-7 breast cancer cells while providing controlled release characteristics. These results highlighted the potential of HAp-based systems as drug delivery platforms for breast cancer treatment (Kırbıyık et al., 2022).

In addition to hydroxyapatite-based formulations, polymeric microsphere systems have also been investigated for targeted drug delivery in breast cancer. In particular, folate-mediated albumin microspheres have been developed to enhance targeting toward folate receptor-expressing tumor cells (Zha et al., 2022). This example shows the potential of ligand-mediated targeting in microsphere-based systems, although such targeting approaches should be distinguished from systemic tumor targeting by intravenously administered HAp microspheres.

## ***6.2. Targeted Delivery Systems for Breast Cancer***

One of the main advantages of microsphere-based delivery systems is the controlled release of drugs, however, selective accumulation at tumor sites still remains a major challenge. Sustained drug release alone cannot ensure optimal therapeutic efficacy unless sufficient amounts of the therapeutic agent reach the tumor site and are efficiently internalized by cancer cells. Hence, considerable efforts have focused on incorporating targeting ligands to improve cellular recognition and receptor-mediated uptake thereby improving therapeutic selectivity and reducing off-target effects (Yao et al., 2020).

Among these approaches, folic acid-mediated targeting has received considerable attention. Zha et al. developed folate-modified albumin microspheres and reported enhanced targeting efficiency toward folate receptor-positive cancer cells. Their findings demonstrated that folic acid modification significantly improved cellular uptake and therapeutic effectiveness compared with non-targeted formulations (Zha et al., 2022). These results demonstrate the potential of ligand-mediated targeting to complement controlled drug release through improved cellular internalization.

However, because folate receptor alpha (FR $\alpha$ ) expression is not consistently high in this disease subtype, the justification for folic acid-mediated targeting in HER2-positive breast cancer needs to be carefully considered. Cheung et al. reported FR $\alpha$  expression in 15.6% of HER2-positive

tumors, compared with 36.8% of triple-negative breast cancers (TNBC). According to PAM50 molecular classification, FR $\alpha$  expression was observed in 10.7% of HER2-positive tumors and 33.3% of basal-like tumors (Cheung et al., 2018). These findings suggest that folate receptor-mediated targeting may be relevant to a subset of HER2-positive tumors with sufficient FR $\alpha$  expression rather than representing a universal targeting strategy for this subtype. O'Shannessy et al. similarly reported an association between FR $\alpha$  receptors and TNBC, further supporting the heterogeneous expression of this receptor across breast cancer subtypes (O'Shannessy et al., 2012). As a result, folic acid and trastuzumab combination shouldn't be seen as inherently better than HER2 targeting alone. As an alternative, in tumors that co-express HER2 and FR $\alpha$ , a dual-ligand approach might offer enhanced receptor engagement, which would enhance cellular recognition and uptake. Preclinical studies using gold nanoclusters functionalized with both folic acid and trastuzumab have reported enhanced cellular accumulation and therapeutic effects compared with non-targeted or single-targeted systems (Samani et al., 2020). However, whether this potential cooperative effect provides a meaningful advantage over single-ligand systems in HAp-based microspheres remains to be experimentally determined.

To better visualize these design principles and related molecular interactions with two illustrative figures, Figure 1 below presents a schematic representation of the hydroxyapatite microsphere detailing its porous surface and drug loadings. Furthermore, to address the biological spatial requirements discussed here, Figure 2 schematically compares the HER2 interaction with the spatial geometry of each ligand system, plotted to scale.

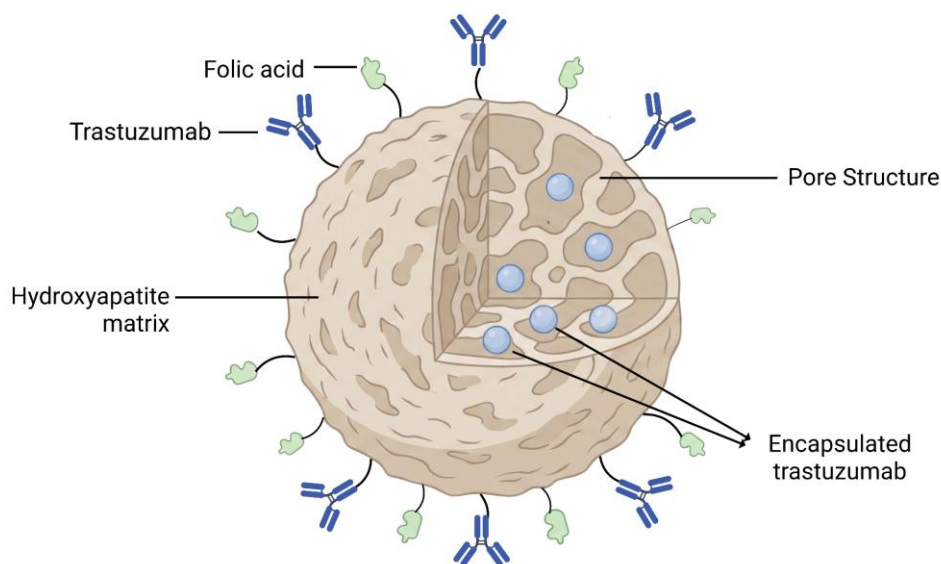


**Figure 1** Schematic representation of the dual-functionalized hydroxyapatite (HAp) microsphere.

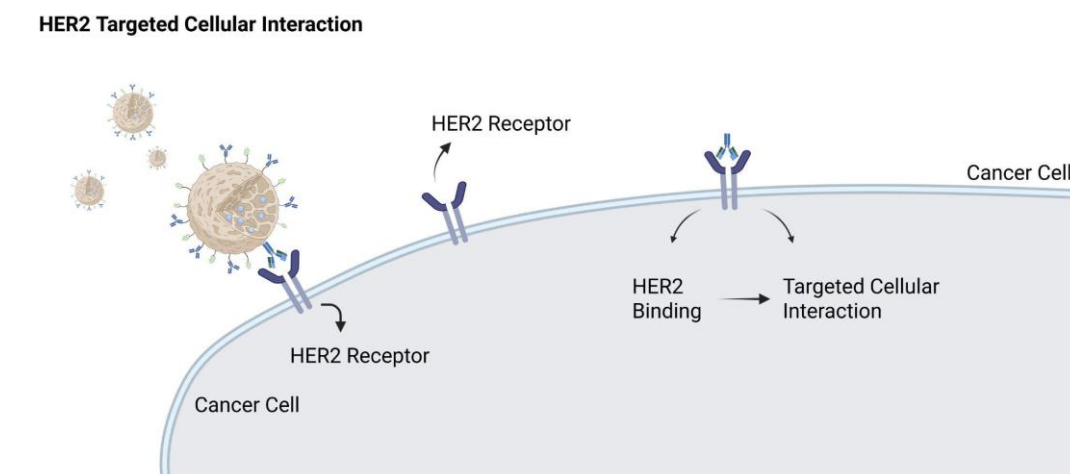


**Figure 2** Mechanism of HER2 receptor-mediated interactions

For the literature examples of folic acid- and antibody-mediated targeting strategies investigated in different carrier systems are summarized in Table 2, including their targeting approaches, conjugation strategies, cellular models, and reported uptake outcomes.

**Table 2** Representative folic acid- and antibody-functionalized drug delivery systems

| Carrier                 | Targeting strategy       | Ligand density / Modification degree | Conjugation chemistry                                                                       | Cell line         | Fold-change in uptake vs. non-targeted control  | Major findings                                                                                                                                                                        | Ref                   |
|-------------------------|--------------------------|--------------------------------------|---------------------------------------------------------------------------------------------|-------------------|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Albumin microspheres    | Folic acid               | 28.1% modification rate              | EDC/Sulfo-NHS-mediated conjugation                                                          | MCF-7             | Not reported                                    | Folate modification enhanced cellular uptake and increased the inhibitory effect of nintedanib on MCF-7 cells.                                                                        | (Zha et al., 2022)    |
| HSA nanoparticles       | Trastuzumab              | 14.92 ± 1.34 µg/mg nanoparticle      | NHS-PEG5000-Mal-mediated covalent coupling                                                  | SK-BR-3 and MCF-7 | Not reported                                    | Trastuzumab-functionalized nanoparticles showed specific binding and intracellular uptake in HER2-overexpressing SK-BR-3 cells, whereas binding was marginal in HER2-low MCF-7 cells. | (Anhorn et al., 2008) |
| Polymeric nanoparticles | Folic acid + trastuzumab | Not reported                         | DCC-NHS mediated conjugation of folic acid and EDC-NHS-mediated conjugation for trastuzumab | MCF-7 and BT-474  | Not reported                                    | Dual-targeted nanoparticles exhibited greater cellular uptake than non-targeted and single-targeted formulations.                                                                     | (Kumar et al., 2017)  |
| Gold nanoclusters       | Folic acid + trastuzumab | Not reported                         | EDC-NHS-mediated conjugation                                                                | SK-BR-3 and L929  | 3-fold for dual-targeted vs. non-targeted AuNCs | Dual-targeted AuNCs showed approximately threefold higher cellular uptake in SK-BR-3 cells and produced greater radiosensitization than non-targeted or single-targeted systems.      | (Samani et al., 2020) |

| Carrier                                         | Targeting strategy       | Ligand density / Modification degree                                     | Conjugation chemistry                        | Cell line        | Fold-change in uptake vs. non-targeted control  | Major findings                                                                                                                                                           | Ref                   |
|-------------------------------------------------|--------------------------|--------------------------------------------------------------------------|----------------------------------------------|------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Polymersomes                                    | Folic acid + trastuzumab | 63.8 µg/mg trastuzumab for PLA-Dox-Her and 58.4 µg/mg for PLA-Dox-FA-Her | EDC/NHS-mediated conjugation                 | MCF-7 and BT-474 | ~9-fold vs. non-targeted polymersomes in BT-474 | Dual-functionalized polymersomes showed enhanced cellular uptake and antitumor activity compared with non-targeted and single-targeted formulations.                     | (Lale et al., 2015)   |
| Trastuzumab-conjugated iron oxide nanoparticles | Trastuzumab              | Half-chain trastuzumab                                                   | Covalent conjugation to nanoparticle surface | SK-BR-3          | Not reported                                    | Trastuzumab conjugated nanoparticles showed high HER2-specific binding and internalization in SK-BR-3 cells, demonstrating the potential of antibody-mediated targeting. | (Truffi et al., 2018) |

The studies summarized in Table 2 demonstrate that folic acid- and antibody-mediated targeting strategies have been investigated across a range of carrier platforms, with several studies reporting enhanced cellular uptake compared with non-targeted formulations. Among these approaches, antibody-mediated targeting has become an important strategy to increase the selectivity of breast cancer drug delivery. Trastuzumab is of particular interest due to its specific recognition of HER2 and its ability to bind HER2 and serve as a targeting ligand for HER2-positive breast cancer cells (Samani et al., 2020). However, the role of trastuzumab within a carrier system can vary depending on the targeted delivery strategy. These different roles and their effects on HAp-based delivery systems are considered in the following discussion.

Despite these promising advances, the bulk of targeted drug delivery research has been focused on polymeric nanoparticles rather than hydroxyapatite-based microspheres. However, the potential of HAp microspheres as carriers for receptor-targeted therapeutics is not exploited sufficiently. For example, the combination of controlled drug release and ligand-mediated targeting represents a developing research area with significant promise for the development of next-generation breast cancer therapies.

Although these advances are promising, there are still several important challenges before active targeting strategies can be effectively translated to hydroxyapatite-based microsphere systems. HAp microspheres have been mainly used for the delivery of small-molecule therapeutics, such as doxorubicin, tamoxifen, vancomycin, and ciprofloxacin (Daryan et al., 2025; Kırbıyık et al., 2022; Wu et al., 2022, 2024), and the application of HAp microspheres for delivery of biomacromolecules, especially monoclonal antibodies, remains limited. Similarly, although systems functionalized with folic acid and HER2-targeted delivery platforms have shown promising potential in cancer therapy, FA-functionalized HAp systems have also been investigated for targeted drug delivery, whereas the integration of folic acid and HER2-targeted strategies into a single HAp-based carrier represents a comparatively unexplored approach (Liu et al., 2019; Verma et al., 2020).

Overall, available reports suggest that active targeting combined with drug delivery represents a promising strategy for HAp-based microsphere systems in HER2-positive breast cancer. However, the use of trastuzumab—as a therapeutic cargo, a surface-bound targeting ligand, or potentially a component of a combined architecture—should be clearly defined according to the intended delivery strategy. Further studies are required to preserve the biological activity of

the antibody, determine the optimal architecture, and validate therapeutic efficacy through extensive preclinical and clinical investigations.

### ***6.2.1. Distinct Roles of Trastuzumab in HAp-based Delivery Systems***

Trastuzumab can be incorporated into HAp-based delivery systems through two distinct design strategies: as a therapeutic cargo or as a surface-bound targeting ligand. These approaches differ in their primary objectives and should be considered separately.

In the first strategy, trastuzumab is incorporated into the HAp carrier as a therapeutic agent and is intended to be released in a controlled manner. The feasibility of using HAp as a carrier for proteins has been demonstrated in several studies. Matsumoto et al. reported that protein adsorbed onto HAp particles could be released in a controlled manner, with the release behavior influenced by HAp solubility and the amount of adsorbed protein (Matsumoto et al., 2004). Similarly, HAp-containing microsphere systems have been investigated for protein delivery using double-emulsion approaches. Ho et al. demonstrated that HAp-containing PLGA microspheres could efficiently entrap BSA and provide sustained protein release, supporting the potential of HAp-containing microspheres for the delivery of therapeutic proteins (Ho et al., 2008). Therefore, the primary objective of using trastuzumab as a therapeutic cargo is to ensure the preservation of the antibody during its incorporation into the carrier and subsequently achieve its controlled release while maintaining its biological activity.

In the second strategy, the aim is to immobilize trastuzumab on the surface of the HAp carrier and enable it to function primarily as a HER2-targeting ligand rather than as a releasable therapeutic cargo. Trastuzumab functionalized carriers have been widely investigated for HER2-targeted drug delivery, with surface conjugation strategies designed to promote preferential interaction with HER2-overexpressing cancer cells (Nieto et al., 2020). In this strategy, the therapeutic payload is located within the carrier, whereas surface-bound trastuzumab facilitates receptor recognition and cellular interaction. Surface functionalization of HAp with biomolecules is also feasible through interactions between HAp surface ions and functional groups present in biological molecules, providing opportunities for the development of ligand-functionalized HAp systems (Kataoka et al., 2024).

The two strategies therefore serve different purposes. The cargo-based approach primarily aims to use HAp as a carrier for the controlled delivery of trastuzumab, whereas the surface-functionalized approach uses trastuzumab to provide HER2-mediated targeting for another therapeutic payload. A combined structure in which trastuzumab contributes to both therapeutic activity and targeting may also be conceptually possible; however, such a design would require careful consideration of antibody orientation, structural stability, and preservation of biological activity.

## **7. Challenges and Limitations**

One of the major limitations involves achieving consistent drug loading efficiency while maintaining controlled release characteristics. Variations in microsphere morphology, pore structure, and particle size may significantly influence drug encapsulation and release kinetics (Sable et al., 2024).

Another important challenge is related to the delivery of biomacromolecules such as monoclonal antibodies. Unlike conventional small-molecule drugs, therapeutic antibodies possess complex three-dimensional structures that are more susceptible to structural instability during carrier fabrication and encapsulation. Processing conditions must therefore be carefully controlled to preserve protein stability and biological activity (Iafisco et al., 2012; Kim & Pack, 2006).

Targeting efficiency also remains a critical concern. Although folic acid-mediated targeting has demonstrated improved cellular uptake in experimental studies, variations in folate receptor expression among different tumor types may affect therapeutic outcomes (Sudimack & Lee, 2000; Tagde et al., 2020). Similarly, HER2-targeted therapies such as trastuzumab may encounter challenges related to heterogeneous treatment responses and therapeutic resistance, which can affect long-term treatment outcomes (Gu et al., 2024).

Beyond the biological challenges, reproducibility in manufacturing and large scale production remain critical obstacles to clinical translation of HAp-based systems. Maintaining consistent particle size distribution, porosity, drug-loading efficiency, and release characteristics across production batches can be challenging, especially during the scale-up of experimental HAp-based formulations (Veiga et al., 2023).

Furthermore, many studies investigating HAp-based delivery systems remain at the preclinical stage. Comprehensive in vivo evaluations, long-term toxicity assessments, pharmacokinetic investigations, and clinical trials are still lacking. Consequently, the clinical translation of promising laboratory-scale formulations remains an important challenge (Sable et al., 2024; Santos et al., 2017).

Another significant limitation is the limited number of studies integrating multiple targeting mechanisms within a single hydroxyapatite-based carrier system. Although HAp-based systems incorporating active targeting ligands and controlled drug release have been investigated (Liu et al., 2019; Verma et al., 2020), the integration of multiple receptor-mediated targeting mechanisms within a single HAp-based carrier remains comparatively underexplored.

## **8. Future Perspectives**

The combination of advanced biomaterials, targeted delivery approaches, and biologically active therapeutics may contribute to the future development of HAp-based drug delivery systems. In particular, the development of stimuli-responsive HAp carriers responsive to tumor-associated triggers such as pH, enzymatic activity, or redox conditions may enable more precise control of drug release and potentially reduce systemic exposure (Mondal et al., 2018; Qian et al., 2023).

Another promising research direction is to expand the application of HAp microspheres from the delivery of conventional small-molecule drugs to biologics such as peptides, proteins, nucleic acids, and monoclonal antibodies. The immobilization of biomacromolecules into HAp-based delivery systems may require further optimization of surface functionalization and loading strategies to preserve biomolecular stability and biological activity (Iafisco et al., 2012; Kim & Pack, 2006).

For HER2-positive breast cancer, combining active targeting strategies with multifunctional HAp carriers represents a promising avenue for future research. In particular, the combination of folic acid-mediated targeting with HER2-directed therapeutics such as trastuzumab may provide complementary approaches to enhance tumor selectivity and controlled drug delivery (Nieto et al., 2020; Sudimack & Lee, 2000). Further advances in biomaterials engineering and targeted drug delivery may facilitate the development of multifunctional HAp-based therapeutic platforms for precision breast cancer treatment.

## 9. Conclusion

Hydroxyapatite microspheres represent a versatile platform because of their porous structure, tunable surface properties, and capacity to accommodate therapeutic agents while enabling controlled release. Recent studies in surface functionalization and targeted delivery have expanded their potential for multifunctional therapeutic systems.

Although folic acid-mediated targeting and HER2-targeted therapies such as trastuzumab offer an attractive framework for the treatment of HER2-positive breast cancer, standard production, maintenance of antibody stability, and rigorous in vivo verification are required to bridge the gap between laboratory synthesis and clinical application.

## Declarations

### *Ethics Statement*

This study did not involve human participants, human-derived data or samples, or live animals; therefore, ethics committee approval was not required. The study was conducted in accordance with generally accepted research and publication ethics.

### *Conflict of Interest*

The authors declare there are no competing interests.

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