مجلۀ علوم طبّی غالب

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پوهنتون غالب

ISSN
E: 3006-094X

دورۀ دوم، شمارۀ اول، بهار و تابستان سال ۱۴۰۴، صص۱۱۳-۱۲۳

رویکردهای بیوشیمیایی اخیر در درمان سرطان: یک مطالعه مروری

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اطلاعات مقاله

نوع مقاله: مروری

تاریخ دریافت: ۲۵/ ۰۹/ ۱۴۰۳

تاریخ پذیرش: ۲۸/ ۱۲/ ۱۴۰۳

تاریخ نشر: ۳۰/ ۰۱/ ۱۴۰۴

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کُد اختصاصیِ مقاله/ DOI:

https://doi.org/10.58342/ghalibMj.V.2.I.1.12

چکیده

زمینه و هدف: پیشرفت‌های اخیر در حوزه بیوشیمی به‌طور چشمگیری چشم‌انداز درمان سرطان را دگرگون کرده است. روش‌های سنتی مانند شیمی‌درمانی و پرتودرمانی، با وجود اثربخشی نسبی، اغلب فاقد ویژگی‌مندی هستند و باعث بروز سمیت‌های سیستمیک می‌شوند. در مقابل، راهکارهای بیوشیمیایی با هدف قرار دادن دقیق مکانیسم‌های مولکولی مؤثر در بروز و پیشرفت تومور، درمان‌هایی هدفمند و کم‌عارضه ارائه می‌دهند. این مقاله مروری به بررسی نوآوری‌های نوین در درمان بیوشیمیایی سرطان می‌پردازد؛ با تمرکز بر مکانیسم‌ها، پتانسیل بالینی و چالش‌های مرتبط با آن‌ها.

روش بررسی: مطالعه‌ای جامع بر روی مقالات علمی اخیر انجام شد که موضوعاتی مانند مهارکننده‌های مولکولی هدفمند، درمان‌های آنزیمی، فناوری‌های ویرایش ژن نظیر (CRISPR-Cas) ، درمان‌های مبتنی بر RNA، بازبرنامه‌ریزی متابولیکی، و سامانه‌های نانوفناورانه در رسانش دارو را پوشش می‌دهد.

یافته‌ها: رویکردهای نوین بیوشیمیایی در درمان سرطان توانسته‌اند دقت درمانی را افزایش، عوارض جانبی را کاهش، و نتایج درمانی بیماران را بهبود بخشند. به‌ویژه، ویرایش ژنی مبتنی بر CRISPR، خاموش‌سازی ژن‌های سرطانی با استفاده از siRNA و نانوذرات چندکاره برای رسانش هدفمند دارو، افق‌های نوینی را در انکولوژی دقیق گشوده‌اند.

نتیجه‌گیری: درمان‌های بیوشیمیایی در حال تبدیل انکولوژی به دانشی فردمحور و کم‌تهاجمی هستند. با اینکه چالش‌هایی نظیر ناهمگونی توموری، محدودیت‌های رسانش، اثرات ناخواسته و هزینه‌های بالا همچنان وجود دارند، پژوهش‌های در حال پیشرفت و تلفیق میان‌رشته‌ای نویدبخش موفقیت‌های بالینی در آینده نزدیک خواهند بود.

واژه‌گانِ کلیدی: درمان سرطان، درمان بیوشیمیایی، کریسپر، نانودارو، مهارکننده‌های هدفمند، درمان‌های RNA

ارجاع به این مقاله: ابراهیمی ن.ا، جامی خ.ج.ا، صالحی م.ا. رویکردهای بیوشیمیایی اخیر در درمان سرطان: یک مطالعه مروری. مجلۀ علوم طبی غالب. [اینترنت]. ۱۹ اپریل ۲۰۲۵. [تاریخ برداشت]؛ ۲(۱): ۱۱۳-۱۲۳: https://doi.org/10.58342/ghalibMj.V.2.I.1.12

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GHALIB MEDICAL JOURNAL

MJ

https://mj.ghalib.edu.af/index.php/mj

OPEN ACCESS

Vol. 2, Issue. 1, Spring & Summer 2025. pp 113-123

ISSN
E: 3006-094X

Recent biochemical approaches in cancer treatment: a review

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Article Information

Type: Review

Received: 15/ 12/ 2024
Accepted: 18/ 03/ 2025
Published: 19/ 04/ 2025

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DOI:
https://doi.org/10.58342/ghalibMj.V.2.I.1.12

Abstract

Background: Recent advancements in biochemistry have significantly reshaped the landscape of cancer therapy. Traditional treatments like chemotherapy and radiotherapy, while effective, often lack specificity and induce systemic toxicity. In contrast, biochemical strategies aim to precisely target molecular mechanisms underlying tumor development and progression.

Methods: This review aims to highlight the latest biochemical innovations in cancer treatment, focusing on their mechanisms, clinical potential, and associated challenges.
A comprehensive analysis of recent peer-reviewed literature was conducted, covering topics such as targeted molecular inhibitors, enzyme-based therapies, gene editing technologies (e.g., CRISPR-Cas), RNA-based therapeutics, metabolic reprogramming, and nanotechnology-enhanced drug delivery systems.

Results: Emerging biochemical modalities have shown promise in improving treatment specificity, minimizing adverse effects, and enhancing patient outcomes. Notably, CRISPR-mediated gene editing, siRNA-based silencing of oncogenes, and multifunctional nanoparticles for targeted drug delivery have opened new frontiers in precision oncology.

Conclusion: Biochemical cancer therapies are transforming oncology into a more personalized and less invasive discipline. Although challenges such as tumor heterogeneity, delivery barriers, off-target effects, and cost remain, ongoing research and interdisciplinary integration hold great promise for future clinical success.

Key words: Cancer therapy, Biochemical treatment, CRISPR, Nanomedicine, Targeted inhibitors, RNA therapeutics

To cite this article: Ebrahimi N.A, Jami kh.j.A, Salehi M. E. Recent Biochemical Approaches in Cancer Treatment: A Review. [Internet]. April 19, 2025. [taking date]; 2(1): 113-123: https://doi.org/10.58342/ghalibMj.V.2.I.1.12

Introduction

Cancer remains one of the leading causes of death worldwide, despite significant advances in diagnosis and treatment. Conventional therapies, such as chemotherapy and radiation, often lack specificity and can lead to severe side effects due to damage to healthy tissues. In recent years, advances in biochemistry have opened new avenues for more targeted and effective cancer treatments.

Modern biochemical approaches focus on understanding cancer at the molecular level, including altered metabolic pathways, enzyme functions, signaling cascades, and interactions between cancer cells and their microenvironment. These insights have enabled the development of therapies that are more precise, less toxic, and in many cases, personalized to individual patients' genetic and biochemical profiles.

This review aims to explore the latest biochemical strategies in cancer therapy, including enzyme-targeted drugs, metabolic inhibitors, biochemical biomarkers, and emerging tools like CRISPR and nanotechnology. By highlighting recent progress in this field, we seek to underline the growing importance of biochemical innovations in the ongoing fight against cancer.

Methodology

This review article employs a comprehensive literature analysis methodology to evaluate recent biochemical approaches in cancer treatment. The analysis focuses on peer-reviewed journal articles, clinical trial reports, and scientific publications from 2000 to the present. Key areas of investigation include enzyme-based therapies, gene editing techniques (such as CRISPR-Cas), RNA-based therapies, metabolic reprogramming strategies, and the application of nanotechnology in drug delivery. The selected studies were assessed based on their relevance, experimental design, clinical outcomes, and innovation in addressing challenges in cancer treatment. This qualitative approach provides an in-depth understanding of current advancements and their future potential in precision oncology.

Biochemical targets in cancer cells

Cancer cells exhibit numerous biochemical alterations that distinguish them from normal cells. These changes include dysregulated signaling pathways, altered enzyme activities, increased reactive oxygen species (ROS) production, and a shift in energy metabolism known as the Warburg effect.

One of the most prominent targets is the PI3K/AKT/mTOR pathway, which regulates cell proliferation, survival, and metabolism. Aberrant activation of this pathway is found in many cancers and is associated with resistance to apoptosis and uncontrolled growth [1].

Another key target is the MAPK/ERK pathway, which transmits mitogenic signals and is frequently upregulated in cancers with RAS or BRAF mutations [2].

Additionally, cancer cells often overexpress specific enzymes such as matrix metalloproteinases (MMPs), which degrade the extracellular matrix and facilitate invasion and metastasis [3]. Targeting such enzymes offers a strategy to hinder tumor progression.

Metabolic reprogramming is also a hallmark of cancer. Many tumor cells rely on aerobic glycolysis for ATP production despite oxygen availability, a phenomenon described by Otto Warburg [4]. This metabolic switch provides both energy and biosynthetic precursors needed for rapid cell proliferation.

Understanding these biochemical distinctions is essential for designing therapies that selectively target malignant cells while sparing healthy tissues.

Enzyme-based therapies in cancer treatment

Enzymes play a pivotal role in the initiation, progression, and survival of cancer cells, making them attractive targets for therapeutic intervention. Enzyme-based therapies either inhibit enzymes that are overactive in cancer or employ enzymes to activate prodrugs selectively within the tumor microenvironment.

1. **Enzyme inhibition**

Certain enzymes are significantly overexpressed in tumors, contributing to their proliferation and invasiveness. For example:

- Tyrosine kinases such as EGFR and HER2 are frequently activated in cancers like non-small cell lung cancer and breast cancer. Their inhibition by drugs like Gefitinib or Trastuzumab has shown remarkable clinical success [5].
- Histone deacetylases (HDACs) modify chromatin structure and regulate gene expression. HDAC inhibitors such as Vorinostat and Romidepsin are used in treating T-cell lymphomas [6].

- Poly (ADP-ribose) polymerase (PARP) enzymes are involved in DNA repair. PARP inhibitors like Olaparib selectively kill cancer cells deficient in BRCA1/2 genes, exploiting a concept known as synthetic lethality [7].

2. Enzyme-activated prodrugs

Some strategies use non-toxic prodrugs that are selectively activated by enzymes abundant in cancer cells:

- Glucuronidase-activated prodrugs rely on β-glucuronidase, which accumulates in tumor tissues due to necrosis and inflammation. These prodrugs remain inactive in healthy tissues, minimizing systemic toxicity [8].
- Gene-directed enzyme prodrug therapy (GDEPT) involves transfecting tumor cells with a gene encoding a non-human enzyme, such as cytosine deaminase, followed by administration of a prodrug like 5-fluorocytosine. The enzyme converts the prodrug into a cytotoxic compound only within the tumor [9].

3. Enzymes as drug delivery tools

Enzymes can also be engineered to selectively cleave drug carriers, such as enzyme-responsive nanoparticles, which release their payload upon encountering specific tumor-associated enzymes like MMPs or cathepsins. Enzyme-based therapies exemplify how biochemical knowledge can be leveraged to increase treatment precision, reduce off-target effects, and improve overall outcomes in oncology.

Metabolic pathway inhibitors in cancer therapy

Cancer cells undergo profound metabolic reprogramming to meet their increased demands for energy and biosynthesis. This hallmark, often referred to as metabolic plasticity, offers multiple biochemical targets for therapeutic intervention.

1. Targeting glycolysis

The Warburg effect, preference for aerobic glycolysis over oxidative phosphorylation, is a well-established feature of many tumors. Inhibiting glycolytic enzymes can starve cancer cells of ATP and key intermediates.

Hexokinase 2 (HK2), overexpressed in many cancers, catalyzes the first step of glycolysis. Inhibitors like 3-bromopyruvate (3-BP) have shown tumor-selective cytotoxicity in preclinical models [10].

Lactate dehydrogenase A (LDHA) converts pyruvate to lactate. LDHA inhibitors are being explored for their ability to block lactate production and reduce tumor acidification and invasiveness [11].

2. Targeting glutamine metabolism

Many tumors exhibit glutamine addiction, relying on glutamine as a key carbon and nitrogen source.
Glutaminase (GLS) converts glutamine to glutamate, feeding the TCA cycle. The GLS inhibitor CB-839 (Telaglenastat) is currently in clinical trials for renal cell carcinoma and triple-negative breast cancer [12].

Transaminases and glutamate dehydrogenase are also being evaluated as indirect metabolic targets to disrupt nitrogen recycling in tumor cells.

3. Targeting lipid metabolism

Rapidly dividing cancer cells require lipids for membrane synthesis and signaling.

Fatty acid synthase (FASN) is frequently upregulated in prostate, breast, and ovarian cancers. Inhibiting FASN disrupts membrane formation and leads to apoptosis [13].
ATP-citrate lyase (ACLY) and acetyl-CoA carboxylase (ACC), key enzymes in de novo fatty acid synthesis, are also potential targets under investigation [14].

4. Targeting mitochondrial function

Despite their reliance on glycolysis, many cancer cells retain functional mitochondria.

Isocitrate dehydrogenase 1/2 (IDH1/2) mutations in gliomas and acute myeloid leukemia (AML) result in the production of oncometabolites such as 2-hydroxyglutarate. Targeting mutant IDH enzymes with drugs like Ivosidenib and Enasidenib has shown clinical benefit [15].

By disrupting cancer-specific metabolic dependencies, these inhibitors can selectively impair tumor growth while sparing normal cells. The metabolic flexibility of tumors, however, necessitates combination strategies and precise patient stratification.

Biochemical biomarkers in targeted cancer therapy

Biochemical biomarkers are measurable molecules found in tissues, blood, or other body fluids that indicate normal or pathological processes, or responses to therapy. In oncology, they are essential for diagnosis, prognosis, treatment selection, and monitoring of therapeutic efficacy.

1. Diagnostic biomarkers

Biochemical biomarkers aid in the early detection and classification of cancers:

Prostate-specific antigen (PSA) is a well-known biomarker for prostate cancer screening, though its use is tempered by concerns over specificity and overdiagnosis [16].

Alpha-fetoprotein (AFP) is elevated in hepatocellular carcinoma and certain germ cell tumors, serving as a serum-based tool for detection and follow-up [17].

Cancer Antigen 125 (CA-125) is used primarily in ovarian cancer management, often in combination with imaging and clinical findings [18].

2. Prognostic and predictive biomarkers

These biomarkers help stratify patients based on likely disease outcome or response to specific treatments.

HER2/neu amplification predicts response to trastuzumab and other HER2-targeted therapies in breast and gastric cancers [19].

KRAS mutation in colorectal cancer is associated with resistance to EGFR inhibitors like cetuximab and panitumumab, making it a negative predictive biomarker [20].

Estrogen receptor (ER) and progesterone receptor (PR) status in breast cancer not only define tumor biology but also guide hormonal therapy [21].

3. Companion diagnostics and precision medicine

Advances in molecular biology have led to the co-development of drugs and their companion diagnostics. These include:

Programmed death-ligand 1 (PD-L1) expression guiding the use of immune checkpoint inhibitors (e.g., pembrolizumab) in non-small cell lung cancer [22].

BCR-ABL fusion gene in chronic myeloid leukemia (CML), the target of tyrosine kinase inhibitors like imatinib [23].

BRCA1/2 mutation status, which predicts responsiveness to PARP inhibitors and also informs hereditary cancer risk [24].

4. Liquid biopsy biomarkers

Non-invasive approaches such as liquid biopsy offer real-time insights into tumor dynamics using:

Circulating tumor DNA (ctDNA), which reflects genetic mutations in tumors and is useful in monitoring treatment response or detecting minimal residual disease [25].

Exosomes and circulating microRNAs, emerging as next-generation biomarkers for early detection and prognostication [26].

The integration of biochemical biomarkers into clinical oncology is revolutionizing cancer care by enabling tailored, efficient, and less toxic therapies. Continuous discovery and validation of novel biomarkers are critical for expanding the reach of personalized medicine.

CRISPR and gene editing approaches in cancer therapy

Gene editing technologies, particularly CRISPR-Cas9, have revolutionized molecular biology by enabling precise, efficient, and cost-effective modifications to the genome. In oncology, these tools offer new avenues for understanding tumor biology and developing targeted treatments.

1. Mechanism of CRISPR-Cas9

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) is derived from a bacterial immune system that uses Cas9 endonuclease guided by a small RNA to introduce double-strand breaks at specific genomic loci. This break can be repaired by:

- Non-homologous end joining (NHEJ), often introducing insertions or deletions (indels).
- Homology-directed repair (HDR), allowing precise gene correction or insertion.

2. CRISPR for cancer gene knockout

Many oncogenes and drug-resistance genes can be disrupted using CRISPR:

PD-1 gene knockout in T-cells enhances their anti-tumor activity by preventing immune exhaustion. Early-phase clinical trials have demonstrated safety and feasibility in non-small cell lung cancer [27].

- EGFR and KRAS editing has been employed in vitro to suppress proliferation in glioblastoma and colorectal cancer models [28].

- NRAS and BRAF targeting is being explored in melanoma to reverse MAPK pathway-driven tumorigenesis [29].

3. Gene correction and synthetic lethality

CRISPR can restore tumor suppressor function or exploit synthetic lethality:
Re-expression of p53 or BRCA1/2 genes using HDR restores DNA damage response and apoptosis [30].
Synthetic lethal interactions, such as BRCA1-deficient tumors and PARP inhibition, can be enhanced or mimicked by editing parallel pathways to sensitize cancer cells to specific therapies [31].

4. CRISPR screens for drug discovery

Genome-wide CRISPR knockout (CRISPRko) or activation (CRISPRa) screens have identified:

- Novel drug targets, such as metabolic enzymes, transcription factors, and epigenetic regulators.
- Resistance mechanisms, e.g., loss of PTEN conferring resistance to immunotherapy [32].

5. Delivery challenges and ethical considerations

Efficient and tumor-specific delivery remains a major obstacle:

- Lentiviral and AAV vectors, while effective in vitro, pose risks of insertional mutagenesis and immune response in vivo.
- Lipid nanoparticles (LNPs) and exosome-based delivery are being optimized for safer systemic administration [33].

Ethically, gene editing in somatic cells for therapeutic purposes is generally accepted, but germline modifications raise significant concerns and are subject to strict regulation.
CRISPR-based therapies are still in early clinical development, but their potential to transform cancer treatment, by rewriting the genetic code of cancer cells or empowering immune responses, is immense.

Nanotechnology and biochemical drug delivery systems in cancer

The integration of nanotechnology into cancer therapeutics has enabled the development of sophisticated drug delivery systems that improve specificity, reduce toxicity, and overcome resistance mechanisms. These nanosystems are often designed with biochemical cues to enhance tumor targeting and intracellular delivery.

1. Lipid-based nanocarriers

Liposomes, spherical vesicles composed of phospholipid bilayers, are among the first and most successful nanocarriers in oncology.

Doxil® (pegylated liposomal doxorubicin) was the first FDA-approved nanodrug for ovarian cancer and Kaposi's sarcoma. Pegylation increases circulation time, and liposomal encapsulation reduces cardiotoxicity [34].

Liposomes can be functionalized with ligands (e.g., folate, transferrin) to target cancer cell receptors overexpressed in specific tumors [35].

2. Polymeric nanoparticles

Biodegradable polymers such as polylactic-co-glycolic acid (PLGA) are widely used in nanoparticle design.
These systems allow controlled release of anticancer agents and can be tailored for pH or enzyme-sensitive drug release in the tumor microenvironment [36].
Docetaxel-loaded PLGA nanoparticles have shown superior antitumor activity and reduced systemic toxicity compared to free drug [37].

3. Inorganic nanoparticles

Metal-based and silica nanoparticles provide unique advantages in imaging and therapy.

Gold nanoparticles (AuNPs) are used for photothermal therapy, converting near-infrared light into heat to kill cancer cells. They can also be conjugated with drugs and targeting molecules [38].

Iron oxide nanoparticles, due to their magnetic properties, can be guided to tumors and serve as MRI contrast agents or hyperthermia triggers [39].

4. Stimuli-responsive nanosystems

Smart nanocarriers respond to internal or external stimuli to release payloads precisely.

pH-responsive systems exploit the acidic tumor microenvironment (pH ~6.5) to release drugs selectively.

Redox-sensitive carriers respond to elevated glutathione levels in cancer cells, ensuring intracellular drug delivery [40].

Temperature-sensitive liposomes release drugs upon mild hyperthermia, synchronizing with local radiation or ultrasound treatments [41].

5. Biomimetic and targeted delivery

Exosome-mimetic vesicles, derived from natural membranes, evade immune clearance and can deliver siRNA, miRNA, or chemotherapeutics [42].

Antibody-drug conjugates (ADCs) combine targeting precision of monoclonal antibodies with potent cytotoxins. Trastuzumab emtansine (T-DM1) is a successful example for HER2-positive breast cancer [43].

Nanotechnology thus offers a biochemical and physical toolkit for engineering precise, efficient, and personalized cancer therapies. The future lies in integrating diagnostics and therapy (theranostics) into a single nanosystem.

Sphingolipid-mediated pathways in cancer therapy

Sphingolipids, essential components of eukaryotic cell membranes, have emerged as critical regulators in cancer biology. Among them, ceramide and sphingosine-1-phosphate (S1P) play opposing roles in cell fate decisions: ceramide promotes apoptosis and cell cycle arrest, while S1P supports proliferation, angiogenesis, and survival. This dynamic balance, often referred to as the "sphingolipid rheostat," is tightly regulated and represents a promising therapeutic target in oncology. Recent biochemical strategies focus on modulating sphingolipid metabolism using agents such as ceramide analogs, sphingosine kinase inhibitors, and S1P receptor modulators to restore apoptotic signaling in cancer cells. Notably, several preclinical and clinical studies have demonstrated the potential of sphingolipid-targeting approaches to overcome chemoresistance and enhance the efficacy of conventional anticancer therapies, highlighting the relevance of lipid signaling pathways in the development of next-generation cancer treatments [44–46].

Challenges and future perspectives in biochemical cancer therapy

While recent advancements in biochemical strategies for cancer treatment have significantly improved outcomes, several scientific, technical, and ethical challenges remain. Addressing these issues will be critical for translating laboratory success into widespread clinical benefit.

1. Tumor heterogeneity and resistance

Cancer is not a single disease but a collection of disorders with significant intra- and inter-tumoral heterogeneity. This complexity leads to:

- Variable drug responses among patients.
- Adaptive resistance mechanisms, such as upregulation of alternative signaling pathways or efflux pumps.

Biochemical therapies must be combined with comprehensive omics profiling and adaptive treatment regimens to account for dynamic tumor evolution [47].

2. Drug delivery and bioavailability

Although nanocarriers and targeting ligands have improved drug delivery, penetration into solid tumors, particularly those with hypoxic cores and dense stroma, remains limited.

- Efforts are ongoing to develop multi-stage delivery systems, where nanoparticles can change size or surface characteristics in response to the tumor microenvironment [48].
- Personalized pharmacokinetics, aided by AI models, may optimize dosage and timing.

3. Safety, off-target effects, and immunogenicity

Gene editing and RNA-based therapeutics raise concerns about:

- Off-target genetic alterations, potentially leading to secondary malignancies.
- Immune responses against synthetic molecules or viral vectors.
- Cytokine release syndrome (CRS) in some immunotherapy approaches.

Thorough preclinical safety evaluations and engineered precision systems are crucial to reduce these risks [49].

4. Cost and accessibility

Many cutting-edge therapies remain prohibitively expensive, limiting access in low- and middle-income countries.

There is an urgent need to promote scalable manufacturing, technology transfer, and public-private partnerships to democratize access to innovative therapies [50].

5. Integrative and precision oncology

Future cancer therapy will likely be multimodal, combining:

- Biochemical therapies (e.g., inhibitors, gene therapy)
- Immunotherapy
- Radiotherapy and surgery
- Digital health technologies (AI diagnostics, remote monitoring)

Emerging fields such as systems biology, single-cell sequencing, and quantum-inspired modeling will further refine our understanding of cancer networks and enable truly individualized medicine [51].

6. Regulatory and ethical frameworks

As technologies evolve, so must the ethical and legal frameworks surrounding them.

Regulatory agencies must balance innovation with safety, particularly for gene editing and AI-assisted diagnostics.

Ethical considerations include informed consent, data privacy, and long-term monitoring of genetically modified patients.

Discussion

Recent advances in biochemical strategies have significantly reshaped the paradigm of cancer treatment. Unlike conventional therapies such as chemotherapy and radiotherapy, which often lack specificity and cause systemic toxicity, modern biochemical approaches enable more precise targeting of cancer-specific molecular mechanisms. Innovations like CRISPR-based gene editing, siRNA-mediated gene silencing, and multifunctional nanoparticles have opened new frontiers in precision oncology.

However, several challenges remain. Tumor heterogeneity, drug resistance, delivery barriers, and the high cost of emerging therapies continue to hinder widespread clinical application. Moreover, while promising, some technologies, particularly gene editing and RNA therapeutics, are still in early clinical stages and raise safety and ethical concerns.

The future of cancer treatment will likely involve the integration of biochemical innovations with computational biology, personalized medicine, and nanotechnology. This interdisciplinary convergence offers promising pathways toward individualized, less invasive, and more effective cancer therapies.

Conclusion

Recent advances in biochemical cancer therapy have transformed our approach to one of the most complex and lethal diseases. From targeted inhibitors and immune checkpoint blockade to gene editing and nanomedicine, the field is rapidly moving toward precision and personalization.

Despite significant challenges, including tumor heterogeneity, delivery limitations, and ethical complexities, the future remains promising. The continued integration of biochemistry with computational biology, nanotechnology, and systems medicine will likely redefine cancer care in the coming decades.

Success will depend not only on scientific breakthroughs but also on ensuring global accessibility, ethical integrity, and patient-centered implementation of these powerful tools.

Future directions/Recommendations

1. Expand clinical research to validate the long-term safety and efficacy of novel biochemical therapies.
2. Develop smarter delivery systems that respond to specific tumor microenvironmental cues to enhance drug targeting.
3. Incorporate multi-omics data (e.g., genomics, proteomics, metabolomics) to better tailor treatments to individual patients.
4. Promote interdisciplinary collaboration among biochemists, oncologists, biomedical engineers, and data scientists.
5. Ensure equitable access to advanced therapies in low- and middle-income countries through policy, manufacturing scalability, and global health initiatives.

Conflict of Interest
The authors declare no conflicts of interest related to this study.

Acknowledgements
The authors would like to express their sincere gratitude to Ghalib University-Herat, particularly the Faculty of Medicine and the Scientific Research Center, for their continuous support and provision of academic resources. We also acknowledge the global scientific community whose pioneering research inspired this review.

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