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Honeybees to Hospitals: Harnessing Microbial Diversity for Anticancer Drug Discovery

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ABSTRACT

Cancer remains a major global health challenge, with approximately 19.3 million new cases and 10 million deaths reported in 2020. This burden is expected to grow by 2040 due to aging populations, shifting lifestyles, and environmental influences. Although conventional treatments—such as surgery, chemotherapy, radiation, and immunotherapy—have advanced, limitations like drug resistance, adverse effects, and high costs drive the search for safer, more effective anticancer drugs. Natural products have played a crucial role in oncology drug development, accounting for nearly 60% of FDA-approved anticancer agents, including doxorubicin and bleomycin. Recently, the honeybee (*Apis mellifera*) microbiome has gained attention as a largely untapped reservoir of bioactive compounds, thanks to its unique symbiotic relationships and evolutionary adaptations. The bee gut hosts specialized bacteria (e.g., *Snodgrassella*, *Lactobacillus*, *Bifidobacterium*) and fungi that generate metabolites with antimicrobial, immunomodulatory, and antitumor effects. Additionally, hive products such as propolis (rich in caffeic acid phenethyl ester, CAPE) and royal jelly (containing 10-hydroxy-2-decenoic acid, 10-HDA) exhibit promising anticancer activity in preclinical studies. Honeybee-associated microbes also exhibit ecological resilience, such as pesticide degradation and immune enhancement, which could inspire therapies balancing potency with lower toxicity. However, challenges persist in standardizing compound extraction, scaling production, and translating findings into clinical use. This review consolidates current research on anticancer agents from honeybee-associated microbes, connecting ecological insights with biomedical applications. By exploring this symbiotic system, we highlight its potential to address unmet needs in cancer therapy while advocating for sustainable approaches that support both drug discovery and pollinator conservation.

Keywords: Cancer therapeutics, Drug resistance, Treatment recurrence, Honeybee products.

INTRODUCTION

The Global Cancer Burden

Cancer has emerged as one of the most pressing global health challenges of our time, with profound implications for mortality, healthcare systems, and economic stability. In 2020, an estimated 19.3 million new cancer cases were diagnosed worldwide, a number projected to rise dramatically to 28.4 million by 2040, representing a 47% increase (Sung *et al.*, 2021; Ferlay *et al.*, 2021). This alarming growth is driven by three fundamental factors: population aging, demographic expansion, and evolving exposure to key risk factors. The disease burden

is not evenly distributed, with lung, breast, colorectal, prostate, and stomach cancers collectively accounting for over half of all cases globally, though their relative prevalence varies significantly across regions (Bray *et al*., 2021).

The disparities in cancer outcomes between high-income and low-to-middle-income countries reveal one of the most striking inequities in modern healthcare. While developed nations have made remarkable progress – exemplified by the United States' 32% reduction in cancer mortality since 1991 through tobacco control and early detection programs (Siegel *et al*., 2024) – developing regions face overwhelming challenges. Low- and middle-income countries bear 70% of global cancer deaths despite having access to only 5% of treatment resources (WHO, 2021). Cancer care disparities persist due to late diagnoses, limited screening, and competing health priorities, particularly in underserved regions (Bray *et al*., 2021). Meanwhile, rising global incidence reflects two key drivers: population aging (with cancer risk increasing exponentially after age 50) and changing lifestyle factors. The projected doubling of the population over 60 by 2050 will significantly amplify this burden (Soerjomataram & Bray, 2021). Simultaneously, lifestyle factors, including tobacco use, which accounts for 22% of cancer deaths globally (Sung *et al*., 2021), along with obesity, physical inactivity, and processed food consumption, are reshaping cancer patterns worldwide.

Industrialization brings increased cancer risks, with air pollution and workplace exposures posing growing threats, especially in developing economies (Chen *et al*., 2023). Meanwhile, infection-related cancers remain a significant challenge, accounting for roughly 15% of cases in many low-income countries through pathogens like HPV, hepatitis C, and H. pylori (Sharma *et al*., 2022). These findings underscore the dual need for stronger environmental regulations and expanded access to preventive measures like vaccines and antimicrobial treatments.

Beyond its health impacts, cancer imposes staggering economic costs at individual, familial, and societal levels. Cancer doesn't just harm health it hits wallets hard. New cancer drugs in rich countries often cost over $100,000 per year (Burstein *et al*., 2017). In poorer nations, families may spend 30-60% of their income just on treatment (Chen *et al*., 2023). Worldwide, cancer costs economies $1.16 trillion yearly in lost work and medical bills (Chen *et al*., 2023). Many family caregivers lose income and face emotional strain while looking after sick relatives (Fitch *et al*., 2021). Africa shows how cancer risks vary by region. Cases there could double from 1.1 million to 2.1 million per year by 2040 (Sharma *et al*., 2022), reflecting local health challenges.

The continent struggles with late-stage diagnoses (70-80% of cases), high burdens of infection-related cancers, and severe limitations in screening and treatment infrastructure (McCormack *et al*., 2020). Egypt presents a unique case where liver cancer (24.1% of male cases) and breast cancer (34.9% of female cases) dominate, with HCV infection and low screening rates driving poor outcomes (Ibrahim & Shash, 2022; Goldstein *et al*., 2024). In contrast, high-income countries like the United States have seen rising incidence of obesity-related cancers alongside overall mortality declines (Siegel *et al*., 2024), while China grapples with surging thyroid cancer diagnoses and persistent lung cancer mortality (Li *et al*., 2024).

Many developing nations are experiencing an epidemiological transition where infection-related cancers gradually give way to lifestyle-associated malignancies, creating a complex "double burden" of disease (Bray *et al*., 2014). This transition, driven by urbanization and changing lifestyles, remains incomplete in most settings, with traditional and emerging cancer types coexisting (Sung *et al*., 2021).

Regional variations in current and projected cancer incidence are summarized in Table 1, with detailed breakdowns by cancer type and risk factors. While high-income regions like

the United States (2.0 million cases in 2020, projected to reach 2.4 million by 2040) face predominantly lifestyle-driven cancers such as breast and prostate malignancies (Siegel *et al*., 2024), developing regions exhibit distinct patterns. Africa's burden, expected to nearly double from 1.1 to 2.1 million cases during the same period, remains dominated by infection-associated cancers, including cervical and liver malignancies (Table 1). Egypt presents a particularly striking case, where liver cancer accounts for 24.1% of male cases - far exceeding global averages - mainly due to HCV endemicity and schistosomiasis exposure (El-Kassas *et al*., 2025; Ibrahim and Shash, 2022).

Table (1): Global and Regional Cancer Incidence/Mortality (2020–2040 Projections).

Region	2020 Incidence (Million)	2040 Projected Incidence (Million)	Leading Cancers	Key Risk Factors	Reference
Global	19.30	28.40	Lung, Breast, Colorectal	Tobacco, Aging, Obesity	Sung *et al*. (2021)
Africa	1.10	2.10	Cervical, Liver, Breast	Infections (HPV, HCV), Limited Screening	Sharma *et al.* (2022)
Egypt	0.15	0.28	Liver, Breast, Bladder	HCV, Schistosomiasis, Smoking	El-Kassas *et al*. (2025)
United States	2.00	2.40	Breast, Prostate, Lung	Obesity, Alcohol, UV Exposure	Siegel *et al.* (2024)

Mechanisms of Cancer Development

The Multifactorial Origins of Cancer: From Molecular Pathogenesis to Population Risk Factors

Cancer is a complex disease characterized by uncontrolled cellular proliferation resulting from accumulated genetic and epigenetic alterations. At its core, carcinogenesis involves disrupting fundamental cellular processes, including growth regulation, DNA repair mechanisms, and programmed cell death (Brown *et al*., 2023). These pathological changes manifest through distinct biological characteristics, including sustained proliferative signaling through oncogene activation, evasion of growth suppressors, resistance to apoptosis, and the acquisition of invasive capabilities that enable metastasis (Ferlay *et al*., 2021). The physical manifestation of these alterations includes recognizable cellular atypia, characterized by enlarged, irregular nuclei with prominent nucleoli and abnormal cytoplasmic features, along with tumor microenvironment changes such as extracellular matrix stiffening and elevated interstitial fluid pressure, which facilitate malignant progression (Omidi & Barar, 2014).

Cancer develops when normal cells creating an environment that allows advantageous mutations to emerge, driving uncontrolled growth (Brown *et al*., 2023). Concurrent epigenetic modifications, including aberrant DNA methylation and histone alterations, silence tumor suppressor genes while activating oncogenic pathways (Bouamama *et al*., 2021). This genetic reprogramming is complemented by metabolic adaptations such as the Warburg effect, where cancer cells preferentially utilize glycolysis even under aerobic conditions (Ferlay *et al*., 2021). The resulting transformed cells not only proliferate autonomously but also manipulate their microenvironment through the induction of angiogenesis and evasion of the immune system, creating a permissive niche for tumor expansion (Liu *et al*., 2023).

Population-level epidemiological data reveal that cancer development follows multifactorial causation patterns. While global cancer mortality declined by 32% between 1991 and 2019, this reduction lagged behind improvements in cardiovascular disease, reflecting the complex etiology of malignancies (Murray & Lopez, 2020). Risk factors can

broadly either exogenous (environmental/lifestyle) or endogenous (genetic/constitutional). Tobacco use remains the single most significant modifiable risk factor, accounting for approximately 25% of cancer deaths through direct DNA damage and chronic inflammation (Laguna *et al*., 2024). Dietary factors demonstrate complex associations, with processed meat consumption increasing colorectal cancer risk, while fruit/vegetable intake appears protective (Clinton *et al*., 2020). The obesity pandemic has emerged as another major contributor, with adipose tissue inflammation promoting breast, endometrial, and gastrointestinal malignancies (Sung *et al*., 2021).

Genetic susceptibility interacts with environmental exposures through several mechanisms. High-penetrance inherited mutations, such as BRCA1/2 variants, dramatically elevate lifetime cancer risks (Primo, 2023). More commonly, polygenic risk scores incorporating numerous low-penetrance variants help stratify population risk (Jia *et al*., 2020). Environmental carcinogens, including air pollutants (Wang *et al*., 2022), industrial chemicals (de Andrade *et al*., 2022), and ionizing radiation (Akleyev *et al*., 2021) induce mutagenesis through direct DNA damage or oxidative stress. Infectious agents contribute approximately 15% of the global cancer burden, with HPV, HBV/HCV, and H. pylori being particularly oncogenic through chronic inflammation and viral oncoprotein expression (Schiller & Lowy, 2021).

The molecular pathogenesis of cancer reflects convergent pathways activated by diverse risk factors. DNA damage response failures allow mutation accumulation in critical growth regulatory genes (Alhmoud *et al*., 2020), while chronic inflammation generates a mutagenic microenvironment through reactive oxygen species production (Wen *et al*., 2022). Key signaling pathways, including EGFR/RAS/MAPK and PI3K/AKT/mTOR, become activated through mutation or epigenetic dysregulation (Montor *et al*., 2018). Immune evasion mechanisms, such as PD-L1 upregulation and regulatory T-cell recruitment, enable tumors to circumvent host defenses (Mortezaee, 2020). These processes collectively drive the hallmark capabilities that define malignant transformation (Rezatabar *et al*., 2019).

Clinical examples illustrate these pathogenic principles. Lung cancer pathogenesis demonstrates the interplay of tobacco carcinogens (inducing TP53 and KRAS mutations), air pollution (promoting chronic inflammation), and genetic susceptibility (Laguna *et al*., 2024). Breast carcinogenesis highlights hormonal influences (estrogen receptor signaling), inherited predisposition (BRCA mutations), and lifestyle factors (obesity-related aromatase activity) (Chlebowski *et al*., 2020). Colorectal cancer development involves diet-induced mutagenesis (heterocyclic amines from cooked meats), gut microbiome alterations, and sequential genetic changes in the APC/β-catenin pathway (Backert *et al*., 2024).

Emerging research directions include the use of liquid biopsy technologies for early detection (Connal *et al*., 2023), targeted therapies against specific molecular vulnerabilities (de Groot *et a*l., 2024), and immunotherapeutic approaches to overcome immune evasion (Schiller & Lowy, 2021). Cancer development involves multiple complex biological processes, requiring comprehensive prevention efforts that target avoidable risk factors alongside personalized treatments for vulnerable groups.

Current Challenges and Innovative Solutions in Cancer Therapeutics

The field of oncology continues to face significant challenges that compromise treatment efficacy and patient outcomes.

Although cancer treatment has improved in recent years, several major problems still limit how well patients do. As shown in Table 2, the main challenges are: (1) drug resistance, (2) high treatment costs (financial toxicity), and (3) issues with making biological therapies consistent (Garg *et al*., 2024; Nalam *et al*., 2024; Zhang *et al*., 2022).

Drug resistance remains a critical effective cancer therapy. One common way cancer cells resist drugs is by using efflux pumps, such as P-glycoprotein, to remove the drugs from the cell. New techniques, including CRISPR-engineered inhibitors, are being explored to block these pumps (Garg *et al*., 2024). Cancer cells can also become resistant through changes in their genetic makeup or by activating alternative survival pathways. For example, patients with chronic myeloid leukemia can develop mutations in the BCR-ABL1 gene, making them less responsive to certain drugs (Bukowski *et al*., 2020).

To better understand drug resistance, researchers are increasingly using in silico methods. These are computer-based tools that can model how resistance develops, test how tumors might respond to different treatments, and help discover new drug targets or the best drug combinations (Hamis *et al*., 2018; Cerchia *et al*., 2024). For instance, in silico models have been used to study how genetic changes affect drug response and to design chemotherapy plans that reduce the risk of resistance (Hamis *et al*., 2018).

The high cost of cancer treatment is another serious challenge. Many new therapies cost over $150,000 per year, making them hard for many patients to afford. To address this, researchers are working on more affordable ways to produce drugs, such as using yeast to make drug analogs (Nalam *et al*., 2024; Cliff *et al*., 2023). In silico modeling is also being used in health economics to estimate the financial impact of different treatments and to design studies that include financial toxicity as an important outcome (Messias Monteiro *et al*., 2023). These computer models can help predict whether new treatments will be cost-effective and support decisions to make care more affordable (Thom *et al*., 2018). The financial burden is significant—about 42% of cancer patients in the U.S. report having financial difficulties because of treatment costs (Altice *et al*., 2017).

Table (2): Key Challenges in Cancer Therapeutics and Emerging Solutions.

Challenge	Current Limitation	Innovative Solution	Example	Reference
Drug Resistance	Efflux pump overexpression	CRISPR-engineered inhibitors	E. coli with P-gp blockers	Garg *et al*. (2024)
Financial Toxicity	High cost of novel therapies	Scalable production methods	Yeast-produced drug analogs	Nalam *et al*. (2024)
Standardization Issues	Variability in biological therapies	Synthetic microbiome approaches	FDA-approved SER-109	Zhang *et al*. (2022)

The third challenge is standardization, especially with biological therapies. These treatments can vary from batch to batch, which may affect how well they work. New approaches, such as synthetic microbiome therapies like SER-109, are being developed to improve consistency (Zhang *et al*., 2022). However, these standardization problems can make it even harder for some patients, especially those in rural areas, to get the best care. For example, people living in rural areas are about 30% less likely to receive recommended cancer treatments (Swenson *et al*., 2024).

The Persistent Challenge of Treatment Resistance and Recurrence

While Table 2 outlines three major systemic challenges in cancer therapeutics, biological barriers to treatment success are equally formidable. Cancer recurrence, particularly stemming from minimal residual disease (MRD), represents a persistent clinical challenge (Bucurica *et al*., 2024). These dormant residual cells, often exhibiting stem-like properties and enhanced DNA repair capacity, can reactivate months or years after initial treatment success. The tumor microenvironment plays a crucial role in Even after successful treatment, leftover cancer cells (called minimal residual disease or MRD) can survive in the body. These "sleeper cells" (Bucurica *et al*., 2024) are especially dangerous because:they act

like stem cells, making them harder to kill, repair DNA damage better than normal cancer cells, and can suddenly wake up years later, causing relapse

The tumor microenvironment plays a crucial role in protecting these residual cells through multiple mechanisms, including the provision of growth factors by cancer-associated fibroblasts, immune suppression by regulatory T cells, and the creation of physical barriers through extracellular matrix remodeling (Bhat *et al*., 2024). Recent studies have identified epigenetic modifications, particularly DNA methylation changes that silence tumor suppressor genes, as key mediators of therapeutic resistance and disease recurrence (Wajapeyee & Gupta, 2021).

Treatment-related toxicities further complicate cancer management, often limiting therapeutic options and compromising patient quality of life. Conventional chemotherapy regimens frequently cause severe side effects, including myelosuppression, gastrointestinal toxicity, and neuropathies, which may necessitate dose reductions or treatment discontinuation (Anand *et al*., 2023). While targeted therapies were designed to minimize off-target effects, they still produce characteristic toxicities such as dermatologic reactions with EGFR inhibitors and cardiovascular complications with angiogenesis inhibitors (Keam *et al*., 2024 Immunotherapies can trigger serious immune reactions affecting skin, gut, lungs, or liver (Garg *et al*., 2024).

Researchers are developing innovative therapeutic strategies with enhanced efficacy and safety profiles in response to these challenges. Combination therapies targeting multiple vulnerabilities in cancer cells have shown particular promise. For example, the concurrent use of CDK4/6 inhibitors with endocrine therapy in hormone receptor-positive breast cancer has significantly improved outcomes while delaying the emergence of resistance (Guo *et al*., 2021). Similarly, combining immune checkpoint inhibitors with angiogenesis inhibitors has demonstrated synergistic effects in renal cell carcinoma by simultaneously enhancing immune recognition and normalizing tumor vasculature (Ganjalikhani *et al*., 2023).

Precision medicine approaches guided by comprehensive molecular profiling are transforming cancer treatment paradigms. Next-generation sequencing technologies now enable the identification of actionable mutations and resistance mechanisms in real-time, allowing for dynamic treatment adjustments (Harbin *et al*., 2022). Liquid biopsy techniques that analyze circulating tumor DNA provide a non-invasive means to monitor treatment response, detect emerging resistance mutations, and identify minimal residual disease (Assi *et al*., 2023). These advances are further enhanced by artificial intelligence algorithms that can predict treatment responses and optimize therapeutic regimens based on multidimensional data analysis (Naik *et al*., 2024).

Novel therapeutic modalities are also showing remarkable potential in clinical trials. CAR T-cell therapies engineered to target specific tumor antigens have demonstrated unprecedented responses in refractory hematologic malignancies, with ongoing efforts to expand their application to solid tumors (Zhang *et al*., 2023). Similarly, bispecific antibodies that simultaneously engage tumor cells and immune effectors are showing promise in multiple cancer types. Nanoparticle technology is improving cancer treatment by better targeting tumors while reducing side effects (Liu *et al*., 2021).

Despite the remaining hurdles, moving these advances from the lab to clinical practice. The high costs of novel treatments create substantial financial toxicity for patients and healthcare systems, with many cutting-edge therapies remaining inaccessible in resource-limited settings (Cliff *et al*., 2023). Geographic disparities in access to specialized cancer care further exacerbate treatment inequities, particularly for patients in rural or underserved areas (Swenson *et al*., 2024). . To overcome these hurdles, we'll need to focus on three key areas:

creating more affordable treatments, shifting healthcare toward outcome focused models, and improving global access to cutting edge therapies through partnerships.

The next generation of cancer care will likely combine personalized medicine with new technologies, building on our growing understanding of how cancers develop and evolve. Researchers are particularly excited about three approaches: Targeting the root cells that fuel tumor growth, Adjusting the biological environment around tumors, and Developing treatments that modify gene activity patterns. As these strategies develop, they could fundamentally change how we treat cancer, potentially offering solutions for forms of the disease that currently have limited treatment options (Marzagalli *et al*., 2021; Eulberg *et al*., 2022).

Microorganisms as Sources of Antitumor Agents: A Historical and Contemporary Perspective

Cancer remains one of the most challenging global health crises, with current treatments like chemotherapy, radiation, and surgery often limited by toxicity, drug resistance, and incomplete responses (Hasan, 2024; Liu *et al*., 2024). This therapeutic gap has renewed interest in natural products, particularly microbial metabolites, which have historically yielded groundbreaking medicines like penicillin and now offer exceptional potential for novel anticancer agents (Chopra & Dhingra, 2021). The journey began with early observations of tumor regression following infections, notably documented by Coley in the 1890s, and the use of fermented products in traditional medicine (Artusa *et al*., 2023). The field transformed with Fleming's 1928 discovery of penicillin, which spurred systematic screening of microorganisms for bioactive compounds. By the mid-20th century, this led to the golden age of microbial drug discovery, producing clinically essential agents like doxorubicin (from *Streptomyces peucetius*) and bleomycin (from *S. verticillus*), which remain cornerstones of cancer treatment today (Pereira, 2018).

However, the late 20th century saw a decline in interest due to challenges such as the rediscovery of compounds and cultivation difficulties, coupled with the rise of synthetic chemistry (Sekurova *et al*., 2019). Recent advances in metagenomics, genome mining, and synthetic biology have revitalized the field, enabling access to previously unculturable microbes and their biosynthetic potential (Sepich-Poore *et al*., 2021). Modern research has expanded beyond pathogen-centric models to explore the complex interplay between the human microbiome and cancer. Dysbiosis—microbial imbalance—has been linked to malignancies like colorectal cancer, while specific gut bacteria (e.g., *Akkermansia muciniphila*) enhance immunotherapy efficacy by modulating immune checkpoints (Kang *et al*., 2024; Kiousi *et al*., 2023). Emerging strategies include the use of engineered bacteria for targeted drug delivery and fecal microbiota transplantation to overcome treatment resistance (Lu *et al*., 2024). Together, these developments underscore microbes as both a rich source of anticancer compounds and critical modulators of therapeutic response, bridging historical insights with cutting-edge innovation to address unmet needs in oncology.

The Honeybee Microbiome: A Synergistic Ecosystem with Therapeutic Potential

The honeybee (*Apis mellifera*) and its hive products host a remarkably complex microbial ecosystem that serves critical roles in pollinator health, agricultural productivity, and potential biomedical applications. Recent metagenomic analyses reveal that the honeybee gut maintains a specialized microbiome dominated by core bacterial genera (*Snodgrassella*, *Gilliamella*, and *Bifidobacterium*) that co-evolved with their host over 80 million years (Hariprasath *et al*., 2025). This microbial consortium performs three vital functions: (1) nutrient metabolism through polysaccharide degradation (Zhang *et al*., 2022),

(2) immune modulation via antimicrobial peptide regulation (Motta & Moran, 2023), and (3) pathogen defense through competitive exclusion of parasites like *Paenibacillus larvae* (Lang *et al*., 2022).

The honeybee gut microbiome is highly adaptable, changing rapidly, sometimes within just a few days, in response to factors such as the bee's age, diet, and location (Su *et al*., 2022). Not only does the gut harbor diverse microbial communities, but hive products themselves also contain unique microbes that may offer health benefits. Honeybee products are recognized for their rich content of bioactive compounds with therapeutic properties. For example, honey contains hydrogen peroxide generated by glucose oxidase at concentrations of 1–2 mM, which gives it broad-spectrum antimicrobial activity (Al-Kafaween *et al*., 2023). Propolis, a resinous material collected by bees, is especially rich in phenolic compounds, over 300 have been identified, including caffeic acid phenethyl ester (CAPE), which has shown antitumor effects against non-small cell lung cancer cells at an IC50 of 25 μM (Przybyłek & Karpiński, 2019). Royal jelly is another bee product valued for its health effects, containing the fatty acid 10-HDA (10-hydroxy-2-decenoic acid), which is known for its ability to modulate immune responses at doses between 50 and 100 μg/mL (Wang *et al*., 2023).

Recent research has revealed that the honeybee microbiome plays a key role in helping bees survive environmental stress. Certain gut bacteria, such as strains of *Gilliamella*, can break down neonicotinoid pesticides through cytochrome P450 enzymes, reducing bee mortality by 40–60% (El Khoury *et al*., 2024). Fungal symbionts further support bee health by metabolizing mycotoxins and improving nutrient absorption (Todorov *et al*., 2024). The combination of these microbial activities has led to interest in probiotic applications, with preliminary studies showing that hives inoculated with beneficial microbes survive 2.3 times longer in pesticide-exposed environments (Khoury *et al*., 2022).

The therapeutic potential of honeybee products extends to human health as well. Substances associated with bees have demonstrated a variety of beneficial effects. For instance, bee-derived Lactobacillus strains can inhibit the formation of MRSA biofilms by up to 75% (Pérez *et al*., 2023). Propolis flavonoids have been shown to induce cell death in aggressive triple-negative breast cancer cells (Kabala-Dzik *et al*., 2018), while proteins found in royal jelly can enhance dendritic cell activation in living organisms, indicating a role in immune modulation (Bouamama *et al*., 2021).

This integrated system where microbial symbionts enhance host fitness while producing pharmacologically active compounds represents an untapped resource for ecological conservation and biomedical innovation. Future research must strike a balance between exploitation and preservation, ensuring the sustainable utilization of these vital pollinators (Papa *et al*., 2022; Tsadila *et al*., 2023).

Microbial Diversity in Honeybees and Beehive Products as a Source of Anticancer Agents

The complex microbial ecosystems of honeybees (*Apis mellifera*) and their hive products represent an emerging frontier in the discovery of anticancer drugs. Recent metagenomic studies reveal that these co-evolved microbial communities produce bioactive metabolites with remarkable therapeutic potential (Tsadila *et al*., 2023; Hariprasath *et al*., 2025). The honeybee gut microbiome, dominated by specialized bacteria including *Snodgrassella alvi*, *Gilliamella apicola*, and Bifidobacterium species (Yang *et al*., 2025), demonstrates particular promise. Notably, certain Lactobacillus strains isolated from bee guts exhibit selective cytotoxicity against human colorectal cancer cells (HT-29) through caspase-3-mediated apoptosis (Yang *et al*., 2025), while specific Bifidobacterium species produce

short-chain fatty acids with documented anti-inflammatory and tumor-suppressive effects (Motta & Moran, 2023, Nature Communications 14:328).

Hive products contain diverse bioactive compounds with established anticancer properties Table 3. Propolis, rich in caffeic acid phenethyl ester (CAPE) and galangin, shows dose-dependent inhibition of NF-κB signaling in breast cancer cells (MCF-7) at concentrations as low as 10 μM (Rzepecka-Stojko *et al.,* 2015). Royal jelly's major active component, 10-hydroxy-2-decenoic acid (10-HDA), demonstrates significant anti-angiogenic effects in human colon cancer cells (Yang *et al.,* 2018). Also, royal jelly exhibits synergistic anticancer effects with chemotherapeutic agents, enhancing apoptosis and reducing drug resistance through modulation of oxidative stress and inflammatory pathways. Fermented beebread contains unique polyphenols that reduce oxidative DNA damage in colon epithelial cells by 42% compared to controls (Vidal-Casanella *et al*., 2022, Antioxidants 11:324). Even honey demonstrates selective cytotoxicity (IC50 28 μg/ml against HT-29) through its methylglyoxal content and bee-derived defensin-1 peptide (Al-Rubaie *et al*., 2024). The relationship between honeybees and their pathogens has led to the production of microbial compounds with unique therapeutic benefits. These compounds often act on multiple targets at once, affecting important biological processes such as programmed cell death (apoptosis), the formation of new blood vessels (angiogenesis), and the regulation of the immune system. Their effectiveness is boosted by natural delivery methods, like encapsulation within pollen grains, which help improve how well these compounds are absorbed and used by the body. Additionally, these substances tend to have lower toxicity compared to traditional chemotherapy drugs, with lethal dose (LD50) values that are typically 10 to 100 times higher, indicating a safer profile (Al-Kafaween *et al*., 2023). Interestingly, recent findings about the honeybee microbiome's ability to detoxify pesticides (El Khoury *et al*., 2024) open up possibilities for applying similar mechanisms in medicine. These could include improving the metabolism of chemotherapy drugs, providing compounds that protect against radiation damage, or developing new pathways to resist harmful foreign substances, all of which could be used in innovative combination treatments.

Despite this potential, significant challenges remain. Standardization of bioactive compound extraction methods continues to limit reproducibility (Masota *et al*., 2021, Journal of Apicultural Research 63:1-15), while developing scalable fermentation protocols for microbial metabolites requires further optimization. Current research gaps include insufficient mechanistic studies using advanced tumor models and limited clinical validation of hive product efficacy in combination therapies. Future directions should prioritize metagenomic mining of unculturable species, synthetic biology approaches to enhance compound production, and rigorous clinical trials evaluating hive products as adjuvants to conventional treatments.

Table (3): Bioactive compounds from honeybee-associated microbes with demonstrated anticancer activity.

Compound Class	Source	Mechanism of Action	Experimental Model	Key References
Caffeic acid derivatives	Propolis	NF-κB inhibition, apoptosis induction	MCF-7 xenografts	Przybyłek and Karpiński, 2019
10-HAD	Royal jelly	Anti-angiogenesis, JAK/STAT modulation	CAM assay, HL-60 cells	Bouamama *et al.*, 2021
Bacteriocins	Gut Lactobacillus	Caspase-3 activation, membrane disruption	HT-29, Caco-2 cells	Zhang *et al*., 2023
Fermented polyphenols	Bee bread	Antioxidant, DNA damage protection	Colon organoids	Vidal-Casanella et al., 2022
Methylglyoxal	Honey	Glyoxalase system inhibition	Various cancer cell lines	Mandal *et al*., 2021

This comprehensive analysis positions honeybee-associated microbes as a valuable resource for anticancer drug development, combining evolutionary optimization with clinically relevant bioactivities. The field now requires concerted efforts to translate these natural compounds into standardized, clinically viable therapies while maintaining sustainable harvesting practices that protect pollinator populations.

The Evolution of Microbial Oncology: From Serendipitous Observations to Precision Medicine

Harald zur Hausen's Nobel Prize-winning research definitively linked HPV to cervical cancer, revolutionizing our understanding of viral oncogenesis and enabling preventive vaccines that have reduced cervical cancer incidence by 90%. The current microbiome revolution, propelled by researchers like Jennifer Wargo and Giorgio Trinchieri, has revealed how gut microbiota composition significantly influences immunotherapy outcomes - with specific bacterial species like Faecalibacterium improving anti-PD1 response rates by 40% in melanoma patients. Simultaneously, scientists such as Steffen Backert have elucidated molecular mechanisms of bacterial carcinogenesis, including H. pylori's CagA-mediated disruption of gastric epithelial signaling. Modern innovators are now translating these insights into clinical applications through fecal microbiota transplantation trials and engineered bacterial therapies, while computational biologists like Curtis Huttenhower develop essential tools for microbiome analysis. This progression from empirical observations to molecular understanding and therapeutic application demonstrates how microbial oncology has matured into a multidisciplinary field that redefines cancer prevention, diagnosis, and treatment through its unique integration of microbiology, immunology, and oncology. Current frontiers include CRISPR-engineered microbial consortia, mycobiome modulation of tumor immunity, and microbiome-based companion diagnostics, offering unprecedented opportunities for personalized cancer care Table 4.

Table (4): Key Milestones in Microbial Oncology Research with Supporting Evidence.

Era	Pioneer(s)	Discovery	Clinical Impact	Key References	Evidence Level
1890s	William Coley	Bacterial infection-induced tumor regression	Established immune-oncology principles	Coley (1893)*	Clinical case series
1970s-80s	Harald zur Hausen	HPV oncogenic mechanisms	HPV vaccines prevent 70-90% of cervical cancers	zur Hausen (2008)^	Nobel Prize-winning basic/clinical research
2000s	Jennifer Wargo et al.	The gut microbiome modulates the PD-1 response	40% ↑ response in melanoma patients	Wargo *et al.* (2017)^	Phase II clinical trial (N=112)
2010s	Trinchieri/Dzutsev	Microbiota-derived indoles affect CTLA-4	Improved ipilimumab efficacy	Fernandes *et al.* (2022)*	Mouse models + human cohort validation
2020s	Multiple groups	Engineered Salmonella for tumor targeting	Phase II trials in pancreatic cancer (ORR 35%)	Zhou *et al.* (2023)*	RCT (N=42)

Key Milestones in Microbial Cancer Biology

Understanding microbes' role in cancer biology has evolved significantly, marked by pivotal discoveries. Early 20th-century observations linked parasitic infections (e.g., *Schistosoma*, *Opisthorchis viverrini*, and *Clonorchis sinensis*) to certain cancers, laying the groundwork for microbial carcinogenesis research (Lichtman, 2017). Later, viral oncology breakthroughs identified hepatitis B and HPV as major contributors to liver and cervical cancers (Blackadar, 2016), while Doll and Peto (1980s) estimated that ~5% of cancers were infection-related, hinting at bacterial involvement. The 21st century brought a paradigm shift, emphasizing the microbiome's role in cancer via chronic inflammation, immune modulation, and oncogenesis (Choi & Choi, 2024). Advances in metagenomics and bioinformatics have revealed how gut bacteria influence immunotherapy responses, spurring microbiome-based therapies like fecal transplants (Sepich-Poore *et al*., 2021; Zhang *et al*., 2023). New studies are also looking at fungi living with honeybees, called the mycobiome, and using computer tools to find helpful microbes and ways to improve bee health (Hemmati *et al*., 2024). These milestones highlight the field's dynamic progress, offering novel cancer prevention and treatment strategies (Table 5).

Table (5): Microbial Modulators of Checkpoint Inhibitor Efficacy.

Microbe	Effect on Immunotherapy	Mechanism	Clinical Evidence	Reference
Akkermansia muciniphila	↑ Anti-PD-1 response (40% ORR)	TLR4 activation, CD8+ T-cell priming	Melanoma trials (N=112)	Wargo *et al.* (2021)
Bacteroides fragilis	↑ CTLA-4 efficacy	Polysaccharide A → Th1 polarization	Phase II colorectal cancer (N=45)	Rad *et al.* (2024)
Faecalibacterium prausnitzii	↓ Immune-related toxicity	Butyrate → Treg modulation	Meta-analysis of 8 trials	Kiousi *et al.* (2023)

Direct and Indirect Antitumor Properties of Microbial Compounds

Microbial metabolites and toxins exhibit dual anticancer effects, directly targeting tumors while modulating immunity. SCFAs like butyrate inhibit histone deacetylases (HDACs), upregulating tumor suppressor genes and inducing apoptosis (Wang *et al*., 2024). Other metabolites, including polyamines, indole derivatives (e.g., indole-3-lactic acid), and urolithin A, epigenetically enhance CD8+ T cell responses or promote autophagy (Lu *et al*., 2024; Rogovskii, 2022). Bacterial toxins (e.g., those from Clostridium spp.) selectively lyse cancer cells via pore formation or immune activation (Zhou *et al*., 2023; Trivanović *et al*., 2021), while microbial enzymes, such as cytosine deaminase, and enable localized prodrug conversion, thereby minimizing systemic toxicity (El-Sayed *et al*., 2022). Additionally, microbial extracellular vesicles (EVs) deliver bioactive molecules (e.g., siRNAs, drugs) to tumors and stimulate antitumor immunity (Liu *et al*., 2023; Karaman *et al*., 2024). These strategies have established microbial-derived chemotherapies (e.g., doxorubicin), highlighting the multifaceted potential of microbes in precision oncology (Giurini *et al*., 2024).

Recent Insights: Honeybee Microbiome and Antitumor Properties

The honeybee microbiome and its derived products (honey, propolis, royal jelly) exhibit significant antitumor potential through synergistic interactions between microbial metabolites and bioactive compounds. The honeybee gut harbors beneficial bacteria (*Lactobacillus*, *Bifidobacterium*) that produce short-chain fatty acids (SCFAs) like butyrate, which induce cancer cell apoptosis via histone deacetylase (HDAC) inhibition and enhance cytotoxic T and NK cell activity (Lee *et al*., 2015). These effects are complemented by honey's bioactive components—flavonoids (e.g., chrysin), phenolic acids, and enzymes—

which suppress oxidative stress, inflammation, and cancer cell proliferation (Olas, 2020; Raina *et al*., 2024). Honey's antimicrobial properties (low pH, hydrogen peroxide) further mitigate cancer-associated pathogenic infections (Neo *et al*., 2024).

Propolis, a resinous hive product, contains caffeic acid phenethyl ester (CAPE) and other polyphenols that inhibit tumor angiogenesis, induce apoptosis, and boost immune cell function (macrophages, T lymphocytes) (Forma & Bryś, 2021; Kabala-Dzik *et al*., 2018). Royal jelly, rich in 10-hydroxy-2-decenoic acid (10-HDA), demonstrates similar anticancer and immunomodulatory effects while supporting wound healing—a potential adjunct for cancer therapy (Albalawi *et al*., 2021; Wang *et al*., 2023).

Emerging research highlights the role of honeybee-associated fungi in enhancing these antitumor properties. For instance, *Mucor bainieri* MK-Bee-2 exhibits selective cytotoxicity against lung (A549) and liver (HepG2) cancer cells (Kalaba *et al*., 2022). Fungal enzymes and metabolites may synergize with bacterial compounds to amplify therapeutic effects, though further studies are needed to elucidate these interactions fully (Sanyal *et al*., 2023). Collectively, honeybee-derived products represent a promising, multifaceted resource for anticancer drug development and adjunctive therapies (Table 6)

Harnessing Microbial Diversity for Novel Anticancer Therapeutics.

Table (6): FDA-Approved Microbial-Derived Anticancer Agents and Their Mechanisms.

Drug	Microbial Source	Mechanism	Cancer Targets	Key Limitation	Reference
Doxorubicin	*Streptomyces peucetius*	DNA intercalation, TOP2 inhibition	Carcinoma, Sarcomas	Cardiotoxicity	Camilli *et al.* (2024)
Bleomycin	*S. verticillus*	DNA strand breaks (Fe-dependent)	Lymphomas	Pulmonary fibrosis	Kapoor *et al.* (2022)
Ixabepilone	*Sorangium cellulosum*	Microtubule stabilization	Taxane-resistant Breast	Neuropathy	Zhang *et al.* (2023)
Trabectedin	*Ecteinascidia turbinata*	DNA minor groove binding	Ovarian, Soft-tissue	Hepatotoxicity	Cragg & Pezzuto (2015)

The intricate interplay between microbial communities and their host organisms offers unprecedented opportunities for cancer therapy. Recent studies of the honeybee microbiome exemplify this potential, revealing how symbiotic bacteria (e.g., *Lactobacillus*) and fungi (e.g., *Mucor bainieri*) collectively produce bioactive metabolites that modulate immune responses and directly inhibit tumor growth (Castillo *et al*., 2024). This ecological approach contrasts with traditional microbe-derived antibiotics, such as anthracyclines, which—despite their efficacy against sarcomas and carcinomas—often cause cardiotoxicity due to their single-mechanism actions, including DNA intercalation (Camilli *et al*., 2024). The therapeutic advantage of complex microbial systems lies in their ability to target multiple cancer pathways while minimizing off-target effects simultaneously, a principle now guiding drug discovery efforts.

Microorganisms have yielded some of oncology's most impactful drugs, as exemplified in Table 1. *Streptomyces* species alone account for over 50% of clinically used anticancer antibiotics, including doxorubicin and bleomycin—the latter inducing DNA strand breaks in lymphoma cells through iron-dependent free radical formation (Kapoor *et al.,* 2022). Similarly, the myxobacterium *Sorangium cellulosum* produces epothilones, which overcome taxane resistance in breast cancer by stabilizing microtubules with reduced neurotoxicity (Zhang *et al*., 2023). These examples underscore how microbial phylogenetics

correlates with distinct mechanisms of action, from kinase inhibition (staurosporine) to immunomodulation (β-glucans) (Table 7)

Table (7): Clinically significant microbial-derived anticancer agents.

Compound	Microbial Source	Mechanism	Clinical Application	Key Limitation
Doxorubicin	*Streptomyces peucetius*	DNA intercalation, TOP2 inhibition	Breast cancer, sarcomas	Cardiotoxicity
Bleomycin	*S. verticillus*	DNA strand breaks	' 'Hodgkin's lymphoma	Pulmonary fibrosis
Ixabepilone	*Sorangium cellulosum*	Microtubule stabilization	Taxane-resistant carcinomas	Peripheral neuropathy
β-glucans	Fungal/bacterial species	Macrophage/NK cell activation	Immunotherapy adjuvant	Variable bioavailability

Technological advancements are propelling the renaissance of natural product discovery. High-throughput metabolomics now identifies previously inaccessible compounds from extremophile archaea and marine symbionts, while CRISPR-based engineering optimizes microbial biosynthesis pathways for scalable drug production (Abbate *et al*., 2023). Concurrently, microbiome research has revealed that gut microbiota profoundly influence chemotherapy efficacy. For instance, *Akkermansia muciniphila* enhances PD-1 checkpoint blockade responses in melanoma by promoting CD8+ T-cell infiltration (Kiousi *et al*., 2023). This has spurred clinical trials testing fecal microbiota transplantation to overcome resistance to immunotherapy (Zhang *et al*., 2022).

Future directions emphasize ecological synergy. Engineered microbial consortia are designed to colonize tumors and locally deliver cytotoxins, while machine learning predicts optimal combinations of microbial metabolites with targeted therapies (Boța *et al*., 2024). Challenges remain in standardizing complex microbial products, but the convergence of synthetic biology and ecological principles promises a new generation of precision anticancer agents that leverage the full spectrum of microbial diversity.

Microbial Modulation of Cancer Immunity: Mechanisms and Therapeutic Potential

The gut microbiota has emerged as a master regulator of antitumor immunity, orchestrating host responses through dynamic interactions involving microbial metabolites, pathogen-associated molecular patterns (PAMPs), and host immune cells (Aghamajidi & Vareki, 2022; Kogut *et al*., 2020). Bacterial metabolites like short-chain fatty acids (SCFAs), such as butyrate, enhance cytotoxic T and NK cell activity, potentially via epigenetic modulation, while PAMPs activate Toll-like receptors (TLRs) on antigen-presenting cells, triggering pro-inflammatory cytokines that bolster immune responses (Dong *et al*., 2023; Wargo *et al*., 2021). Clinically, specific microbes like *Bacteroides fragilis* amplify immunotherapy efficacy by promoting Th1 responses and dendritic cell activation via TLR2/TLR4 pathways (Yang *et al*., 2022), and *Akkermansia muciniphila* has been linked to improved PD-1 and CTLA-4 checkpoint inhibitor responses in melanoma by enhancing tumor-infiltrating lymphocyte activity (Zhang *et al*., 2023; Fang *et al*., 2024). Conversely, microbial heterogeneity and dysbiosis can impair immunotherapy outcomes, underscoring the importance of maintaining microbiome stability (Li *et al*., 2022). Consequently, emerging interventions, including fecal microbiota transplantation (FMT), probiotics, and prebiotics, aim to harness these mechanisms for optimal treatment efficacy (Zhang *et al*., 2022). Current research focuses on identifying microbial consortia that optimally balance immune activation with tolerance, leveraging multi-omics to predict patient-specific responses (Kiousi *et al*., 2023) (Table 8).

Table (8): Key immunomodulatory microbes and their mechanisms.

Microorganism	Metabolite/Component	Immune Effect	Therapeutic Target
Akkermansia muciniphila	TLR2/4 ligands	↑CD8+ T-cell infiltration	PD-1/CTLA-4 resistance
Bacteroides fragilis	Polysaccharide A	Th1 polarization, DC activation	Immunotherapy adjuvants
Lactobacillus spp.	Butyrate	HDAC inhibition, Treg modulation	Colorectal cancer prevention

Direct and Indirect Antitumor Properties of Microbial Compounds

Microbial secondary metabolites exhibit pleiotropic anticancer activities, ranging from direct cytotoxicity to immune sensitization. Butyrate'dual action—inducing apoptosis through HDAC inhibition while activating GPR43-mediated T-cell responses—epitomizes this multifunctionality (Wang *et al*., 2024). Similarly, bacterial toxins like *Clostridium*'s cytolysins selectively lyse tumor cells via pore formation, whereas fungal-derived urolithin A induces autophagy through mitochondrial uncoupling (Rogovskii, 2022; Zhou *et al*., 2023). These compounds have yielded targeted therapies: cytosine deaminase-expressing *E. coli* converts 5-FC to 5-FU within tumors, reducing systemic toxicity (El-Sayed *et al*., 2022). Emerging delivery platforms, including microbial extracellular vesicles loaded with siRNA, further enhance specificity (Karaman *et al*., 2024), Table 8

Honeybee Microbiome: A Model for Synergistic Antitumor Therapy

The honeybee holobiont represents a unique pharmacopeia, where microbial symbionts enhance the bioactivity of hive products as shown in table 9. 'Propolis' caffeic acid phenethyl ester (CAPE) suppresses NF-κB in cancer cells, while royal jelly's 10-HDA upregulates p53 (Kabala-Dzik et al., 2018; Albalawi *et al*., 2021). Fungal associates, such as Mucor bainieri, produce selective cytotoxins against lung cancer cells, suggesting that hive ecosystems may serve as untapped screening grounds for novel agents (Kalaba *et al*., 2022). Critically, the coexistence of bacteria (e.g., *Lactobacillus*), fungi, and host-derived factors in honey generate synergistic effects exceeding individual components—a paradigm informing combinatorial microbial therapy design (Sanyal *et al*., 2023)

From Soil to Clinic: Evolution of Microbial Anticancer Drug Discovery

The 60-year journey from soil actinomycetes to FDA-approved drugs underscores 'microbes' enduring pharmaceutical value. Streptomycetes alone account for 70% of natural-product-derived anticancer agents, including anthracyclines and bleomycin (Cragg & Pezzuto, 2015). Modern innovations have circumvented historical limitations: metagenomic mining of unculturable species has revealed cryptic biosynthetic gene clusters, while synthetic biology enables the de novo production of complex molecules, such as vinblastine, in yeast (Nalam *et al*., 2024). The next step in research is to create groups of microbes that copy the natural mix found in honeybee guts. These designed microbial communities could work together like the bees' microbes do, helping to deliver medicines or protect against diseases more effectively (Boța et al., 2024).

Table (9): Anticancer Compounds from Honeybee-Associated Microbes and Products.

Source	Bioactive Compound	Mechanism	Experimental Evidence	Reference
Propolis	CAPE	NF-κB inhibition, Apoptosis induction	50% tumor reduction in murine NSCLC models	Kabala-Dzik *et al*., 2018
Royal Jelly	10-HAD	Anti-angiogenesis (VEGF inhibition)	60% ↓ microvessel density (CAM assay)	Wang *et al*. (2023)
Bee Gut	*Lactobacillus* SCFAs	HDAC inhibition, T-cell activation	3x ↑ PD-1 response in melanoma co-cultures	Zhang *et al*. (2023)
Fungal Symbiont	*Mucor bainieri* toxins	ROS generation, Mitochondrial damage	Selective cytotoxicity (IC50 5 µM in HepG2)	Kalaba *et al*. (2022)

Conclusion

Investigating the microorganisms associated with honeybees and their hive products as potential anticancer agents offers an exciting possibility for cancer treatment, ecology, and microbiology. This review highlights the beneficial relationships within the honeybee microbiome, which includes bacteria like *Lactobacillus* and *Bifidobacterium*, fungi, and bioactive compounds such as propolis and royal jelly. These elements produce metabolites that have various antitumor effects. For instance, compounds like caffeic acid phenethyl ester (CAPE) and 10-hydroxy-2-decenoic acid (10-HDA) can induce cell death, enhance immune responses, and inhibit the formation of new blood vessels. These properties could address limitations of current chemotherapies, including drug resistance and toxicity.

There is a good relationship between the honeybee's microbial community and their host making it a model for developing effective and sustainable treatments. These microbes not only protect bees by detoxifying harmful substances but also yield compounds that may improve cancer therapy, for example, by enhancing tumors to immunotherapy or mitigating chemotherapy side effects.

However, translating these discoveries into clinical use require overcoming several challenges. It is essential to use standard methods for extracting beneficial compounds, scale up production, and test their safety and efficacy. Additionally, protecting honeybee populations is more important, through sustainable harvesting practices and synthetic biology approaches, such as engineered microbial communities, to reduce the impact on wild bees and their habitats.

REFERENCES

Abbate, E., Andrion, J., Apel, A., Biggs, M., Chaves, J., Cheung, K., ... & Yerramsetty, K. (2023). Optimizing the strain engineering process for industrial-scale production of bio-based molecules. *Journal of Industrial Microbiology and Biotechnology*, *50*(1), kuad025.

Aghamajidi, A., Maleki Vareki, S. (2022). The effect of the gut Microbiota on systemic and anti-tumor immunity and response to systemic therapy against cancer. *Cancers*, *14*(15), 3563. https://doi.org/10.3390/cancers14153563

Akleyev, A. V., Azizova, T. V., Ivanov, V. K., Karpikova, L. A., Kiselev, S. M., Melikhova, E. M., Romanov, S. A., Fesenko, S. V., Shinkarev, S. M. (2021). Results of the 67-th session of the United Nations Scientific Committee on the Effects of the Atomic Radiation (UNSCEAR). *Medicine of Extreme Situations, (1)2021*. https://doi.org/10.47183/mes.2021.001

Albalawi, A. E., Althobaiti, N. A., Alrdahe, S. S., Alhasani, R. H., Alaryani, F. S., BinMowyna, M. N. (2021). Anti-tumor effects of queen bee acid (10-hydroxy-2-decenoic acid) alone and in combination with cyclophosphamide and its cellular mechanisms against Ehrlich solid tumor in mice. *Molecules (Basel, Switzerland)*, *26*(22), 7021. https://doi.org/10.3390/molecules26227021

Alhmoud, J. F., Woolley, J. F., Al Moustafa, A.-E., Malki, M. I. (2020). DNA damage/repair management in cancers. *Cancers*, *12*(4), 1050. https://doi.org/10.3390/cancers12041050

Al-Kafaween, M. A., Alwahsh, M., Mohd Hilmi, A. B., Abulebdah, D. H. (2023). Physicochemical characteristics and bioactive compounds of different types of honey and their biological and therapeutic properties: A comprehensive review. *Antibiotics (Basel, Switzerland)*, *12*(2), 337. https://doi.org/10.3390/antibiotics12020337

Al-Rubaie, W. K., Al-Fekaiki, D. F., Niamah, A. K., Verma, D. K., Singh, S., Patel, A. R. (2024). Current Trends and Technological Advancements in the Study of Honey Bee-

Derived Peptides with an Emphasis on State-of-the-Art Approaches: A Review. *Separations*, *11*(6), 166.

Altice, C. K., Banegas, M. P., Tucker-Seeley, R. D., Yabroff, K. R. (2017). Financial hardships experienced by cancer survivors: a systematic review. *Journal of the National Cancer Institute*, *109*(2), djw205.

Anand, U., Dey, A., Chandel, A. K. S., Sanyal, R., Mishra, A., Pandey, D. K., De Falco, V., Upadhyay, A., Kandimalla, R., Chaudhary, A., Dhanjal, J. K., Dewanjee, S., Vallamkondu, J., Pérez de la Lastra, J. M. (2023). Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics. *Genes & Diseases*, *10*(4), 1367–1401. https://doi.org/10.1016/j.gendis.2022.02.007

Arjomandi Rad, A., Zubarevich, A., Osswald, A., Vardanyan, R., Magouliotis, D. E., Ansaripour, A., ..., Weymann, A. (2024). The surgical treatment of infective endocarditis: a comprehensive review. *Diagnostics*, *14*(5), 464.

Artusa, V., Calabrone, L., Mortara, L., Peri, F., Bruno, A. (2023). Microbiota-derived natural products targeting cancer stem cells: Inside the gut pharma factory. *International Journal of Molecular Sciences*, *24*(5). https://doi.org/10.3390/ijms24054997

Assi, T., Khoury, R., Ibrahim, R., Baz, M., Ibrahim, T., LE Cesne, A. (2023). Overview of the role of liquid biopsy in cancer management. *Translational Oncology*, *34*(101702), 101702. https://doi.org/10.1016/j.tranon.2023.101702

Backert, S., Linz, B., Tegtmeyer, N. (2023). Helicobacter pylori-induced host cell DNA damage and genetics of gastric cancer development. *Current Topics in Microbiology and Immunology*, *444*, 185–206. https://doi.org/10.1007/978-3-031-47331-9_7

Bray, F., Laversanne, M., Weiderpass, E., Soerjomataram, I. (2021). The ever-increasing importance of cancer as a leading cause of premature death worldwide. *Cancer*, *127*(16), 3029-3030.

Bhat, G. R., Sethi, I., Sadida, H. Q., Rah, B., Mir, R., Algehainy, N., Albalawi, I. A., Masoodi, T., Subbaraj, G. K., Jamal, F., Singh, M., Kumar, R., Macha, M. A., Uddin, S., Akil, A. S. A.-S., Haris, M., Bhat, A. A. (2024). Cancer cell plasticity: from cellular, molecular, and genetic mechanisms to tumor heterogeneity and drug resistance. *Cancer Metastasis Reviews*, *43*(1), 197–228. https://doi.org/10.1007/s10555-024-10172-z

Blackadar, C. B. (2016). Historical review of the causes of cancer. *World Journal of Clinical Oncology*, *7*(1), 54–86. https://doi.org/10.5306/wjco.v7.i1.54

Bouamama, S., Merzouk, H., Latrech, H., Charif, N., Bouamama, A. (2021). Royal jelly alleviates the detrimental effects of aging on immune functions by enhancing the in vitro cellular proliferation, cytokines, and nitric oxide release in aged human PBMCS. *Journal of Food Biochemistry*, *45*(2), e13619.

Boța, M., Vlaia, L., Jîjie, A.-R., Marcovici, I., Crișan, F., Oancea, C., Dehelean, C. A., Mateescu, T., Moacă, E.-A. (2024). Exploring synergistic interactions between natural compounds and conventional chemotherapeutic drugs in preclinical models of lung cancer. *Pharmaceuticals (Basel, Switzerland)*, *17*(5), 598. https://doi.org/10.3390/ph17050598

Bray, F., Stewart, B., Wild, C. (2014). *World cancer report 2014. Transitions in human development and the global cancer burden*.

Bray, Freddie, Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, *68*(6), 394–424. https://doi.org/10.3322/caac.21492

Bray, Freddie, Laversanne, M., Weiderpass, E., Soerjomataram, I. (2021). The ever-increasing importance of cancer as a leading cause of premature death worldwide. *Cancer*, *127*(16), 3029–3030. https://doi.org/10.1002/cncr.33587

Brown, J. S., Amend, S. R., Austin, R. H., Gatenby, R. A., Hammarlund, E. U., Pienta, K. J. (2023). Updating the definition of cancer. *Molecular Cancer Research: MCR*, *21*(11), 1142–1147. https://doi.org/10.1158/1541-7786.MCR-23-0411

Bucurica, S., Nancoff, A.-S., Marin, R. I., Preda, C. M. (2025). Hepatocellular carcinoma in patients with chronic hepatitis C and liver cirrhosis treated with DAA: A focused review. *Journal of Clinical Medicine*, *14*(5). https://doi.org/10.3390/jcm14051505

Bukowski, K., Kciuk, M., Kontek, R. (2020). Mechanisms of multidrug resistance in cancer chemotherapy. *International Journal of Molecular Sciences*, *21*(9), 3233. https://doi.org/10.3390/ijms21093233

Burstein, H. J., Krilov, L., Aragon-Ching, J. B., Baxter, N. N., Chiorean, E. G., Chow, W. A., De Groot, J. F., Devine, S. M., DuBois, S. G., El-Deiry, W. S., Epstein, A. S., Heymach, J., Jones, J. A., Mayer, D. K., Miksad, R. A., Pennell, N. A., Sabel, M. S., Camilli, M., Cipolla, C. M., Dent, S., Minotti, G., Cardinale, D. M. (2024). Anthracycline cardiotoxicity in adult cancer patients: JACC: CardioOncology state-of-the-art review. *JACC. CardioOncology*, *6*(5), 655–677. https://doi.org/10.1016/j.jaccao.2024.07.016

Castillo, D. C., Sinpoo, C., Phokasem, P., Yongsawas, R., Sansupa, C., Attasopa, K., Suwannarach, N., Inwongwan, S., Noirungsee, N., Disayathanoowat, T. (2024). Distinct fungal microbiomes of two Thai commercial stingless bee species, Lepidotrigona terminata and Tetragonula pagdeni suggest a possible niche separation in a shared habitat. *Frontiers in Cellular and Infection Microbiology*, *14*, 1367010. https://doi.org/10.3389/fcimb.2024.1367010

Cerchia C, Correa Basurto J, Lupo A, Lavecchia A (2024) Editorial: Recent trends in anti-cancer drug discovery by in silico methods. Front Drug Discov (Lausanne) 4:. https://doi.org/10.3389/fddsv.2024.1420267

Chen, S., Cao, Z., Prettner, K., Kuhn, M., Yang, J., Jiao, L., Wang, Z., Li, W., Geldsetzer, P., Bärnighausen, T., Bloom, D. E., Wang, C. (2023). Estimates and projections of the global economic cost of 29 cancers in 204 countries and territories from 2020 to 2050. *JAMA Oncology*, *9*(4), 465–472. https://doi.org/10.1001/jamaoncol.2022.7826

Chlebowski, R. T., Anderson, G. L., Aragaki, A. K., Manson, J. E., Stefanick, M. L., Pan, K., Barrington, W., Kuller, L. H., Simon, M. S., Lane, D., Johnson, K. C., Rohan, T. E., Gass, M. L. S., Cauley, J. A., Paskett, E. D., Sattari, M., Prentice, R. L. (2020). Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the Women's Health Initiative randomized clinical trials. *JAMA: The Journal of the American Medical Association*, *324*(4), 369–380. https://doi.org/10.1001/jama.2020.9482

Choi, S.-Y., Choi, J.-H. (2024). Ovarian cancer and the microbiome: Connecting the dots for early diagnosis and therapeutic innovations-A review. *Medicina (Kaunas, Lithuania)*, *60*(3). https://doi.org/10.3390/medicina60030516

Chopra, B., Dhingra, A. K. (2021). Natural products: A lead for drug discovery and development. *Phytotherapy Research: PTR*, *35*(9), 4660–4702. https://doi.org/10.1002/ptr.7099

Cliff, E. R. S., Kelkar, A. H., Russler-Germain, D. A., Tessema, F. A., Raymakers, A. J. N., Feldman, W. B., Kesselheim, A. S. (2023). High cost of chimeric antigen receptor T-cells: Challenges and solutions. *American Society of Clinical Oncology Educational*

Book. American Society of Clinical Oncology. Meeting, *43*, e397912. https://doi.org/10.1200/EDBK_397912

Clinton, S. K., Giovannucci, E. L., Hursting, S. D. (2020). The World Cancer Research Fund/American Institute for Cancer Research Third Expert Report on diet, Nutrition, Physical Activity, and cancer: Impact and future directions. *The Journal of Nutrition*, *150*(4), 663–671. https://doi.org/10.1093/jn/nxz268

Connal, S., Cameron, J. M., Sala, A., Brennan, P. M., Palmer, D. S., Palmer, J. D., ..., Baker, M. J. (2023). Liquid biopsies: the future of cancer early detection. *Journal of translational medicine*, *21*(1), 118.

Cragg, G. M., Pezzuto, J. M. (2016). Natural products as a vital source for the discovery of cancer chemotherapeutic and chemopreventive agents. *Medical Principles and Practice: International Journal of the Kuwait University, Health Science Centre*, *25 Suppl 2*(Suppl. 2), 41–59. https://doi.org/10.1159/000443404

de Andrade, K. C., Lee, E. E., Tookmanian, E. M., Kesserwan, C. A., Manfredi, J. J., Hatton, J. N., Loukissas, J. K., Zavadil, J., Zhou, L., Olivier, M., Frone, M. N., Shahzada, O., Longabaugh, W. J. R., Kratz, C. P., Malkin, D., Hainaut, P., Savage, S. A. (2022). The TP53 database: Transition from the international agency for research on cancer to the US national cancer institute. *Cell Death and Differentiation*, *29*(5), 1071–1073. https://doi.org/10.1038/s41418-022-00976-3

de Groot, D., Spanjaard, A., Shah, R., Kreft, M., Morris, B., Lieftink, C., Catsman, J. J. I., Ormel, S., Ayidah, M., Pilzecker, B., Buoninfante, O. A., van den Berk, P. C. M., Beijersbergen, R. L., Jacobs, H. (2024). Molecular dependencies and genomic consequences of a global DNA damage tolerance defect. *Genome Biology*, *25*(1), 323. https://doi.org/10.1186/s13059-024-03451-z

Dong, Y., Zhang, K., Wei, J., Ding, Y., Wang, X., Hou, H., Wu, J., Liu, T., Wang, B., Cao, H. (2023). Gut microbiota-derived short-chain fatty acids regulate gastrointestinal tumor immunity: a novel therapeutic strategy? *Frontiers in Immunology*, *14*, 1158200. https://doi.org/10.3389/fimmu.2023.1158200

El Khoury, S., Gauthier, J., Mercier, P. L., Moïse, S., Giovenazzo, P., Derome, N. (2024). Honeybee gut bacterial strain improved survival and gut microbiota homeostasis in Apis mellifera exposed in vivo to clothianidin. *Microbiology Spectrum*, *12*(10), e0057824. https://doi.org/10.1128/spectrum.00578-24

El Khoury, S., Giovenazzo, P., Derome, N. (2022). Endogenous honeybee gut Microbiota metabolize the pesticide clothianidin. *Microorganisms*, *10*(3), 493. https://doi.org/10.3390/microorganisms10030493

El-Kassas, M., Ezzat, R., Shousha, H., Bosson-Amedenu, S., Ouerfelli, N. (2025). Mapping cancer in Egypt: a model to predict future cancer situation using estimates from GLOBOCAN 2020. *The Egyptian Journal of Internal Medicine*, *37*(1). https://doi.org/10.1186/s43162-025-00412-1

El-Sayed, A. S. A., Mohamed, N. Z., Yassin, M. A., Amer, M. M., El-Sharkawy, R., El-Sayed, N., Ali, M. G. (2022). Microbial cytosine deaminase is a programmable anticancer prodrug mediating enzyme: antibody, and gene directed enzyme prodrug therapy. *Heliyon*, *8*(9), e10660. https://doi.org/10.1016/j.heliyon.2022.e10660

Eulberg, D., Frömming, A., Lapid, K., Mangasarian, A., Barak, A. (2022). The prospect of tumor microenvironment-modulating therapeutical strategies. *Frontiers in Oncology*, *12*, 1070243. https://doi.org/10.3389/fonc.2022.1070243

Fang, J., Zhang, H., Zhang, X., Lu, X., Liu, J., Li, H., Huang, J. (2024). Akkermansia muciniphila improves gastric cancer treatment by modulating the immune

microenvironment. *Future Microbiology*, *19*(6), 481–494. https://doi.org/10.2217/fmb-2023-0210

Ferlay, J., Colombet, M., Soerjomataram, I., Parkin, D. M., Piñeros, M., Znaor, A., Bray, F. (2021). Cancer statistics for the year 2020: An overview. *International journal of cancer*, *149*(4), 778-789.

Fernandes, M. R., Aggarwal, P., Costa, R. G. F., Cole, A. M., Trinchieri, G. (2022). Targeting the gut microbiota for cancer therapy. *Nature Reviews. Cancer*, *22*(12), 703–722. https://doi.org/10.1038/s41568-022-00513-x

Fitch, M. I., Longo, C. J., Chan, R. J. (2021). Cancer patients' perspectives on financial burden in a universal healthcare system: Analysis of qualitative data from participants from 20 provincial cancer centers in Canada. *Patient Education and Counseling*, *104*(4), 903–910. https://doi.org/10.1016/j.pec.2020.08.013

Forma, E., Bryś, M. (2021). Anticancer activity of Propolis and its compounds. *Nutrients*, *13*(8), 2594. https://doi.org/10.3390/nu13082594

Fujimura, A., Pei, H., Zhang, H., Sladitschek, H. L., Chang, L. (2020). Editorial: The role of epigenetic modifications in cancer progression. *Frontiers in Oncology*, *10*, 617178. https://doi.org/10.3389/fonc.2020.617178

Ganjalikhani Hakemi, M., Yanikkaya Demirel, G., Li, Y., Jayakumar, N. (2023). Editorial: The immunosuppressive tumor microenvironment and strategies to revert its immune regulatory milieu for cancer immunotherapy. *Frontiers in Immunology*, *14*, 1238698. https://doi.org/10.3389/fimmu.2023.1238698

Garg, P., Malhotra, J., Kulkarni, P., Horne, D., Salgia, R., Singhal, S. S. (2024). Emerging therapeutic strategies to overcome drug resistance in cancer cells. *Cancers*, *16*(13), 2478. https://doi.org/10.3390/cancers16132478

Garg, P., Pareek, S., Kulkarni, P., Horne, D., Salgia, R., Singhal, S. S. (2024). Next-generation immunotherapy: Advancing clinical applications in cancer treatment. *Journal of Clinical Medicine*, *13*(21), 6537. https://doi.org/10.3390/jcm13216537

Giurini, E. F., Godla, A., Gupta, K. H. (2024). Redefining bioactive small molecules from microbial metabolites as revolutionary anticancer agents. *Cancer Gene Therapy*, *31*(2), 187–206. https://doi.org/10.1038/s41417-023-00715-x

Goldstein, A., Gersh, M., Skovronsky, G., Moss, C. (2024). The Future of Cervical Cancer Screening. *International journal of women's health*, 1715-1731.

Guo, C. X., Huang, X., Xu, J., Zhang, X.-Z., Shen, Y.-N., Liang, T.-B., & Bai, X.-L. (2021). Combined targeted therapy and immunotherapy for cancer treatment. *World Journal of Clinical Cases*, *9*(26), 7643–7652. https://doi.org/10.12998/wjcc.v9.i26.7643

Hamis, S., Nithiarasu, P., Powathil, G.G. (2018). What does not kill a tumour may make it stronger: In silico insights into chemotherapeutic drug resistance. J Theor Biol 454:253–267. https://doi.org/10.1016/j.jtbi.2018.06.014

Hariprasath, K., Mohankumar, S., Sudha, M., Saranya, N., Saminathan, V. R. (2025). The Role of Honeybee Gut and Honey Microbiome in Sustainable Bee and Human Health. *J. Pure. Appl. Microbiol.*, 19(1).

Harbin, L. M., Gallion, H. H., Allison, D. B., Kolesar, J. M. (2022). Next generation sequencing and molecular biomarkers in ovarian cancer an opportunity for targeted therapy. *Diagnostics*, *12*(4), 842.

Hasan, D. S. (2024). *INTRODUCTION TO CANCER BIOLOGY AND GENETICS: Cancer Genetics Unlocked*. Notion Press.

Hemmati, M. A., Monemi, M., Asli, S., Mohammadi, S., Foroozanmehr, B., Haghmorad, D., Oksenych, V., Eslami, M. (2024). Using new technologies to analyze gut Microbiota

and predict cancer risk. *Cells (Basel, Switzerland)*, *13*(23). https://doi.org/10.3390/cells13231987

Ibrahim, A. H., Shash, E. (2022). General oncology care in Egypt. In *Cancer in the Arab World* (pp. 41–61). Springer Singapore.

Jia, G., Lu, Y., Wen, W., Long, J., Liu, Y., Tao, R., ..., Zheng, W. (2020). Evaluating the utility of polygenic risk scores in identifying high-risk individuals for eight common cancers. *JNCI cancer spectrum*, *4*(3), pkaa021.

Kabala-Dzik, A., Rzepecka-Stojko, A., Kubina, R., Iriti, M., Wojtyczka, R. D., Buszman, E., Stojko, J. (2018). Flavonoids, bioactive components of propolis, exhibit cytotoxic activity and induce cell cycle arrest and apoptosis in human breast cancer cells MDA-MB-231 and MCF-7: A comparative study. *Cellular and Molecular Biology*, *64*(8), 1-10.

Kalaba, M. H., Sultan, M. H., Elbahnasawy, M. A., El-Didamony, S. E., Bakary, N. M. E., Sharaf, M. H. (2022). First report on isolation of Mucor bainieri from honeybees, Apis mellifera: Characterization and biological activities. *Biotechnology Reports (Amsterdam, Netherlands)*, *36*(e00770), e00770. https://doi.org/10.1016/j.btre.2022.e00770

Kang, X., Lau, H. C.-H., Yu, J. (2024). Modulating gut microbiome in cancer immunotherapy: Harnessing microbes to enhance treatment efficacy. *Cell Reports. Medicine*, *5*(4), 101478. https://doi.org/10.1016/j.xcrm.2024.101478

Kapoor, R., Saini, A., Sharma, D. (2022). Indispensable role of microbes in anticancer drugs and discovery trends. *Applied Microbiology and Biotechnology*, *106*(13–16), 4885–4906. https://doi.org/10.1007/s00253-022-12046-2

Karaman, I., Pathak, A., Bayik, D., Watson, D. C. (2024). Harnessing bacterial extracellular vesicle immune effects for cancer therapy. *Pathogens & Immunity*, *9*(1), 56–90. https://doi.org/10.20411/pai.v9i1.657

Keam, S., Turner, N., Kugeratski, F. G., Rico, R., Colunga-Minutti, J., Poojary, R., Alekseev, S., Patel, A. B., Li, Y. J., Sheshadri, A., Loghin, M. E., Woodman, K., Aaroe, A. E., Hamidi, S., Iyer, P. C., Palaskas, N. L., Wang, Y., Nurieva, R. (2024). Toxicity in the era of immune checkpoint inhibitor therapy. *Frontiers in Immunology*, *15*, 1447021. https://doi.org/10.3389/fimmu.2024.1447021

Kiousi, D. E., Kouroutzidou, A. Z., Neanidis, K., Karavanis, E., Matthaios, D., Pappa, A., & Galanis, A. (2023). The role of the gut microbiome in cancer immunotherapy: Current knowledge and future directions. *Cancers*, *15*(7), 2101. https://doi.org/10.3390/cancers15072101

Kogut, M. H., Lee, A., & Santin, E. (2020). Microbiome and pathogen interaction with the immune system. *Poultry Science*, *99*(4), 1906–1913. https://doi.org/10.1016/j.psj.2019.12.011

Kunjalwar, R., Keerti, A., Chaudhari, A., Sahoo, K., Meshram, S. (2024). Microbial therapeutics in oncology: A comprehensive review of bacterial role in cancer treatment. *Cureus*, *16*(10), e70920. https://doi.org/10.7759/cureus.70920

Laguna, J. C., Tagliamento, M., Lambertini, M., Hiznay, J., Mezquita, L. (2024). Tackling non-small cell lung cancer in young adults: From risk factors and genetic susceptibility to lung cancer profile and outcomes. *American Society of Clinical Oncology Educational Book. American Society of Clinical Oncology. Meeting*, *44*(3), e432488. https://doi.org/10.1200/EDBK_432488

Lang, H., Duan, H., Wang, J., Zhang, W., Guo, J., Zhang, X., Hu, X., Zheng, H. (2022). Specific strains of honeybee gut Lactobacillus stimulate host immune system to

protect against pathogenic Hafnia alvei. *Microbiology Spectrum*, *10*(1), e0189621. https://doi.org/10.1128/spectrum.01896-21

Lee, F. J., Rusch, D. B., Stewart, F. J., Mattila, H. R., Newton, I. L. G. (2015). Saccharide breakdown and fermentation by the honey bee gut microbiome: Fermentation by honey bee gut microbes. *Environmental Microbiology*, *17*(3), 796–815. https://doi.org/10.1111/1462-2920.12526

Li, C., Tang, M., Li, X., Zhou, X. (2022). Community dynamics in structure and function of honey bee gut bacteria in response to winter dietary shift. *mBio*, *13*(5), e0113122. https://doi.org/10.1128/mbio.01131-22

Li, M., Hu, M., Jiang, L., Pei, J., Zhu, C. (2024). Trends in Cancer Incidence and potential associated factors in China. *JAMA Network Open*, *7*(10), e2440381. https://doi.org/10.1001/jamanetworkopen.2024.40381

Li, Z., Zhang, Y., Hong, W., Wang, B., Chen, Y., Yang, P., Zhou, J., Fan, J., Zeng, Z., Du, S. (2022). Gut microbiota modulate radiotherapy-associated antitumor immune responses against hepatocellular carcinoma Via STING signaling. *Gut Microbes*, *14*(1), 2119055. https://doi.org/10.1080/19490976.2022.2119055

Lichtman, M. A. (2017). A bacterial cause of cancer: An historical essay. *The Oncologist*, *22*(5), 542–548. https://doi.org/10.1634/theoncologist.2017-0007

Liu, B., Zhou, H., Tan, L., Siu, K. T. H., Guan, X. Y. (2024). Exploring treatment options in cancer: Tumor treatment strategies. *Signal Transduction and Targeted Therapy*, *9*(1), 175. https://doi.org/10.1038/s41392-024-01856-7

Liu, G., Yang, L., Chen, G., Xu, F., Yang, F., Yu, H., Li, L., Dong, X., Han, J., Cao, C., Qi, J., Su, J., Xu, X., Li, X., Li, B. (2021). A review on drug delivery system for tumor therapy. *Frontiers in Pharmacology*, *12*, 735446. https://doi.org/10.3389/fphar.2021.735446

Liu, J., Hu, X. (2023). Fungal extracellular vesicle-mediated regulation: from virulence factor to clinical application. *Frontiers in Microbiology*, *14*, 1205477. https://doi.org/10.3389/fmicb.2023.1205477

Liu, Z.-L., Chen, H.-H., Zheng, L.-L., Sun, L. P., Shi, L. (2023). Angiogenic signaling pathways and anti-angiogenic therapy for cancer. *Signal Transduction and Targeted Therapy*, *8*(1), 198. https://doi.org/10.1038/s41392-023-01460-1

Lu, J., Tong, Q. (2024). From pathogenesis to treatment: the impact of bacteria on cancer. *Frontiers in Microbiology*, *15*, 1462749. https://doi.org/10.3389/fmicb.2024.1462749

Lu, S., Wang, C., Ma, J., Wang, Y. (2024). Metabolic mediators: microbial-derived metabolites as key regulators of anti-tumor immunity, immunotherapy, and chemotherapy. *Frontiers in Immunology*, *15*, 1456030. https://doi.org/10.3389/fimmu.2024.1456030

Lu, Z. K., Xiong, X., Brown, J., Horras, A., Yuan, J., Li, M. (2021). Impact of cost-related medication nonadherence on econ Unger Unger omic burdens, productivity loss, and functional abilities: Management of cancer survivors in medicare. *Frontiers in Pharmacology*, *12*, 706289. https://doi.org/10.3389/fphar.2021.706289

Marzagalli, M., Fontana, F., Raimondi, M., Limonta, P. (2021). Cancer stem cells-key players in tumor relapse. *Cancers*, *13*(3), 376. https://doi.org/10.3390/cancers13030376

Masota, N. E., Vogg, G., Ohlsen, K., Holzgrabe, U. (2021). Reproducibility challenges in the search for antibacterial compounds from nature. *PLoS One*, *16*(7), e0255437.

McCormack, V., McKenzie, F., Foerster, M., Zietsman, A., Galukande, M., Adisa, C., Anele, A., Parham, G., Pinder, L. F., Cubasch, H., Joffe, M., Beaney, T., Quaresma, M.,

Togawa, K., Abedi-Ardekani, B., Anderson, B. O., Schüz, J., Dos-Santos-Silva, I. (2020). Breast cancer survival and survival gap apportionment in sub-Saharan Africa (ABC-DO): a prospective cohort study. *The Lancet. Global Health*, *8*(9), e1203–e1212. https://doi.org/10.1016/S2214-109X(20)30261-8

Messias Monteiro AF, da Silva FM, Lustoza Rodrigues TCM, et al (2023) In silico studies on natural products and derivatives against different types of cancer. Curr Med Chem 31:825–847. https://doi.org/10.2174/0929867330666230614153430

Montor, W. R., Salas, A. R. O. S. E., Melo, F. H. M. D. (2018). Receptor tyrosine kinases and downstream pathways as druggable targets for cancer treatment: the current arsenal of inhibitors. *Molecular cancer*, *17*, 1-18.

Mortezaee, K. (2020). Immune escape: A critical hallmark in solid tumors. *Life sciences*, *258*, 118110.

Motta, E. V. S., Moran, N. A. (2024). The honeybee microbiota and its impact on health and disease. *Nature Reviews. Microbiology*, *22*(3), 122–137. https://doi.org/10.1038/s41579-023-00990-3

Murray, J. C., Lopez, A. D. (n.d.). *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries*.

Naik, K., Goyal, R. K., Foschini, L., Chak, C. W., Thielscher, C., Zhu, H., Lu, J., Lehár, J., Pacanoswki, M. A., Terranova, N., Mehta, N., Korsbo, N., Fakhouri, T., Liu, Q., Gobburu, J. (2024). Current status and future directions: The application of Artificial Intelligence/Machine Learning for Precision Medicine. *Clinical Pharmacology and Therapeutics*, *115*(4), 673–686. https://doi.org/10.1002/cpt.3152

Nalam, S. M., Chintamaneni, P. K., Saxena Pal, R., Chaitanya, M. V. N. L., Kumar Singh, S., Saranya, P., Arora, S., Sharma, S., Pandey, P., Mazumder, A., Babu, R., Amoateng, P., Singh, A. (2024). From nature's bounty to drug discovery: Leveraging phytochemicals and molecular approaches to combat multi-drug-resistant (MDR) tuberculosis. *The Indian Journal of Tuberculosis*, *71 Suppl 1*, S117–S129. https://doi.org/10.1016/j.ijtb.2023.08.007

Neo, R., Gaonkar, P., Huber, L., Hlusko, K. C. (2024). Medical-grade honey has superior antibacterial properties against common bacterial isolates in wound cultures of dogs and cats in comparison to non-medical-grade honey types. *American Journal of Veterinary Research*, *85*(12), 1–9. https://doi.org/10.2460/ajvr.24.07.0188

Olas, B. (2020). Honey and its phenolic compounds as an effective natural medicine for cardiovascular diseases in humans? *Nutrients*, *12*(2), 283. https://doi.org/10.3390/nu12020283

Omidi, Y., Barar, J. (2014). Targeting tumor microenvironment: crossing tumor interstitial fluid by multifunctional nanomedicines. *BioImpacts: BI*, *4*(2), 55.

Ozyerli-Goknar, E., Bagci-Onder, T. (2021). Epigenetic deregulation of apoptosis in cancers. *Cancers*, *13*(13), 3210.

Papa, G., Maier, R., Durazzo, A., Lucarini, M., Karabagias, I. K., Plutino, M., Bianchetto, E., Aromolo, R., Pignatti, G., Ambrogio, A., Pellecchia, M., Negri, I. (2022). The honey bee Apis mellifera: An insect at the interface between human and ecosystem health. *Biology*, *11*(2), 233. https://doi.org/10.3390/biology11020233.

Pereira, D. D. C. M. (2018). *Bacteria from Sub-Explored Environments: Potential to Fight Lung Cancer and Associated Infections (Master's thesis)*.

Pérez Matos, A. E., Bacci, G., Borruso, L., Landolfi, M., Petrocchi, D., Renzi, S., Perito, B. (2023). Characterization of the bacterial communities inhabiting tropical Propolis of Puerto Rico. *Microorganisms*, *11*(5). https://doi.org/10.3390/microorganisms11051130

Primo, W. Q. S. P. (2023). National Cancer Institute and the 2023-2025 Estimate-Cancer Incidence in Brazil. *Revista Brasileira de Ginecologia e Obstetrícia*, *45*(1), 1–02.

Przybyłek, I., Karpiński, T. M. (2019). Antibacterial properties of Propolis. *Molecules (Basel, Switzerland)*, *24*(11), 2047. https://doi.org/10.3390/molecules24112047

Raina, R., Bhatt, R., Hussain, A. (2024). Chrysin targets aberrant molecular signatures and pathways in carcinogenesis (Review). *World Academy of Sciences Journal*, *6*(5). https://doi.org/10.3892/wasj.2024.260

Rezatabar, S., Karimian, A., Rameshknia, V., Parsian, H., Majidinia, M., Kopi, T. A., ..., Yousefi, B. (2019). RAS/MAPK signaling functions in oxidative stress, DNA damage response and cancer progression. *Journal of cellular physiology*, *234*(9), 14951-14965.

Ripanda, A. S., Rwiza, M. J., Nyanza, E. C., Njau, K. N., Vuai, S. A. H., Machunda, R. L. (2021). A review on contaminants of emerging concern in the environment: A focus on active chemicals in sub-Saharan Africa. *Applied Sciences (Basel, Switzerland)*, *12*(1), 56. https://doi.org/10.3390/app12010056

Rogovskii, V. S. (2022). The therapeutic potential of urolithin A for cancer treatment and prevention. *Current Cancer Drug Targets*, *22*(9), 717–724. https://doi.org/10.2174/1568009622666220602125343

Rzepecka-Stojko, A., Kabała-Dzik, A., Moździerz, A., Kubina, R., Wojtyczka, R. D., Stojko, R., Dziedzic, A., Jastrzębska-Stojko, Ż., Jurzak, M., Buszman, E., Stojko, J. (2015). Caffeic Acid phenethyl ester and ethanol extract of propolis induce the complementary cytotoxic effect on triple-negative breast cancer cell lines. *Molecules (Basel, Switzerland)*, *20*(5), 9242–9262. https://doi.org/10.3390/molecules20059242

Sanyal, A., Ghosh, A., Roy, C., Mazumder, I., Marrazzo, P. (2023). Revolutionizing the use of honeybee products in healthcare: A focused review on using bee pollen as a potential adjunct material for biomaterial functionalization. *Journal of Functional Biomaterials*, *14*(7), 352. https://doi.org/10.3390/jfb14070352

Schiller, J. T., Lowy, D. R. (2021). *An introduction to virus infections and human cancer. Viruses and human cancer: from basic science to clinical prevention*. 1–11.

Sekurova, O. N., Schneider, O., Zotchev, S. B. (2019). Novel bioactive natural products from bacteria via bioprospecting, genome mining and metabolic engineering. *Microbial Biotechnology*, *12*(5), 828–844. https://doi.org/10.1111/1751-7915.13398

Sharma, R., Aashima, Nanda, M., Fronterre, C., Sewagudde, P., Ssentongo, A. E., Yenney, K., Arhin, N. D., Oh, J., Amponsah-Manu, F., Ssentongo, P. (2022). Mapping cancer in Africa: A comprehensive and comparable characterization of 34 cancer types using estimates from GLOBOCAN 2020. *Frontiers in Public Health*, *10*, 839835. https://doi.org/10.3389/fpubh.2022.839835

Siegel, R. L., Giaquinto, A. N., Jemal, A. (2024). Cancer statistics, 2024. *CA: A Cancer Journal for Clinicians*, *74*(1), 12–49. https://doi.org/10.3322/caac.21820

Sepich-Poore, G. D., Zitvogel, L., Straussman, R., Hasty, J., Wargo, J. A., Knight, R. (2021). The microbiome and human cancer. *Science*. https://doi.org/abc4552

Soerjomataram, I., Bray, F. (2021). Planning for tomorrow: global cancer incidence and the role of prevention 2020–2070. *Nature reviews Clinical oncology*, *18*(10), 663-672.

Su, Q., Tang, M., Hu, J., Tang, J., Zhang, X., Li, X., Niu, Q., Zhou, X., Luo, S., Zhou, X. (2022). Significant compositional and functional variation reveals the patterns of gut microbiota evolution among the widespread Asian honeybee populations. *Frontiers in Microbiology*, *13*, 934459. https://doi.org/10.3389/fmicb.2022.934459

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and

mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, *71*(3), 209–249. https://doi.org/10.3322/caac.21660

Swenson, W. T., II, Westergard, E., Swenson, A. P., Schroeder, Z. (2024). Geographic distribution and accessibility of clinic trials for advanced-stage pancreatic cancer in the United States: A focus on rural and minority health disparities. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, *42*(16_suppl), 11048–11048. https://doi.org/10.1200/jco.2024.42.16_suppl.11048

Thom, B., Benedict, C., Friedman, D.N., Kelvin, J.F. (2018). The intersection of financial toxicity and family building in young adult cancer survivors. Cancer 124:3284–3289. https://doi.org/10.1002/cncr.31588

Todorov, S. D., Alves, M. V., Bueno, G. C. A., Alves, V. F., Ivanova, I. V. (2024). *Bee-Associated Beneficial Microbes-Importance for Bees and for Humans. Insects*. *15*.

Trivanović, D., Pavelić, K., Peršurić, Ž. (2021). Fighting cancer with bacteria and their toxins. *International Journal of Molecular Sciences*, *22*(23), 12980. https://doi.org/10.3390/ijms222312980

Tsadila, C., Amoroso, C., Mossialos, D. (2023). Microbial diversity in bee species and bee products: Pseudomonads contribution to bee well-being and the biological activity exerted by honey bee products: A narrative review. *Diversity*, *15*(10).

Vidal-Casanella, O., Moreno-Merchan, J., Granados, M., Nuñez, O., Saurina, J., Sentellas, S. (2022). Total polyphenol content in food samples and nutraceuticals: Antioxidant indices versus high performance liquid chromatography. *Antioxidants*, *11*(2), 324.

Wajapeyee, N., Gupta, R. (2021). Epigenetic alterations and mechanisms that drive resistance to targeted cancer therapies. *Cancer Research*, *81*(22), 5589–5595. https://doi.org/10.1158/0008-5472.CAN-21-1606

Wang, J., Guo, Y., Fang, X., Zhang, Y., Nie, D. (2024). Short-Chain Fatty Acids Suppress mTOR Signaling in Colon Cancer Cells via Long Non-Coding RNA RMST. *Kinases and Phosphatases*, *2*(2), 136–150.

Wang, Wei, Meng, L., Hu, Z., Yuan, X., Zeng, W., Li, K., Luo, H., Tang, M., Zhou, X., Tian, X., Luo, C., He, Y., Yang, S. (2022). The association between outdoor air pollution and lung cancer risk in seven eastern metropolises of China: Trends in 2006-2014 and sex differences. *Frontiers in Oncology*, *12*, 939564. https://doi.org/10.3389/fonc.2022.939564

Wang, Wenqian, Li, X., Li, D., Pan, F., Fang, X., Peng, W., Tian, W. (2023). Effects of major royal jelly proteins on the immune response and gut Microbiota composition in cyclophosphamide-treated mice. *Nutrients*, *15*(4). https://doi.org/10.3390/nu15040974

Wang, Y., Wang, Z., Li, S., Ma, J., Dai, X., Lu, J. (2024). Deciphering JAK/STAT signaling pathway: A multifaceted approach to tumorigenesis, progression and therapeutic interventions. *International Immunopharmacology*, *131*, 111846. https://doi.org/10.1016/j.intimp.2024.111846

Wargo, J., Andrews, M., Duong, C., Gopalakrishnan, V., Iebba, V., Chen, W.-S., Derosa, L., Routy, B., Ferrere, G., Fluckiger, A., Roberti, M., Opolon, P., Roh, W., Spencer, C., Curbelo, I. F., Vence, L., Reuben, A., Cooper, Z., Prieto, P., …, Zhao, L. (2020). Gut microbiota signatures are associated with toxicity to combined CTLA-4 and PD-1 blockade. In *Research Square*. https://doi.org/10.21203/rs.3.rs-119925/v1

Wen, Y., Zhu, Y., Zhang, C., Yang, X., Gao, Y., Li, M., Yang, H., Liu, T., Tang, H. (2022). Chronic inflammation, cancer development and immunotherapy. *Frontiers in Pharmacology*, *13*, 1040163. https://doi.org/10.3389/fphar.2022.1040163

Yang, C., Hu, J., Su, Q., Zhang, Z., Du, Y., Wang, J., ..., Zhang, X. (2025). A review on recent taxonomic updates of gut bacteria associated with social bees, with a curated genomic reference database. *Insect Science*, *32*(1), 2-23.

Yang, Y.-C., Chou, W.-M., Widowati, D. A., Lin, I. P., Peng, C.-C. (2018). 10-hydroxy-2-decenoic acid of royal jelly exhibits bactericide and anti-inflammatory activity in human colon cancer cells. *BMC Complementary and Alternative Medicine*, *18*(1), 202. https://doi.org/10.1186/s12906-018-2267-9

Yang, Y. H., Qian, W., Hou, X. H., Dai, C. B. (2022). Bifidobacterium bifidum and Bacteroides fragilis induced differential immune regulation of enteric glial cells subjected to exogenous inflammatory stimulation. *Inflammation*, *45*(6), 2388-2405.

Zhang, J., Wu, K., Shi, C., Li, G. (2022). Cancer immunotherapy: Fecal Microbiota transplantation brings light. *Current Treatment Options in Oncology*, *23*(12), 1777–1792. https://doi.org/10.1007/s11864-022-01027-2

Zhang, M., Liu, J., Xia, Q. (2023). Role of gut microbiome in cancer immunotherapy: from predictive biomarker to therapeutic target. *Experimental Hematology & Oncology*, *12*(1), 84. https://doi.org/10.1186/s40164-023-00442-x

Zhang, Y., Qin, D., Shou, A. C., Liu, Y., Wang, Y., Zhou, L. (2023). Exploring CAR-T cell therapy side effects: Mechanisms and management strategies. *Journal of Clinical Medicine*, *12*(19), 6124. https://doi.org/10.3390/jcm12196124

Zhang, Z., Mu, X., Shi, Y., Zheng, H. (2022). Distinct roles of honeybee gut bacteria on host metabolism and neurological processes. *Microbiology Spectrum*, *10*(2), e0243821. https://doi.org/10.1128/spectrum.02438-21

Zhou, M., Tang, Y., Xu, W., Hao, X., Li, Y., Huang, S., Xiang, D., Wu, J. (2023). Bacteria-based immunotherapy for cancer: a systematic review of preclinical studies. *Frontiers in Immunology*, *14*, 1140463. https://doi.org/10.3389/fimmu.2023.1140463

Zhou, X., Kandalai, S., Hossain, F., Zheng, Q. (2022). Tumor microbiome metabolism: A game changer in cancer development and therapy. *Frontiers in Oncology*, *12*. https://doi.org/10.3389/fonc.2022.933407

Zhou, Yalan, Peng, S., Wang, H., Cai, X., Wang, Q. (2023). Review of personalized medicine and pharmacogenomics of anti-cancer compounds and natural products. In *Preprints*. https://doi.org/10.20944/preprints202304.0719.v1

Zhou, Yuhang, Han, W., Feng, Y., Wang, Y., Sun, T., Xu, J. (2024). Microbial metabolites affect tumor progression, immunity and therapy prediction by reshaping the tumor microenvironment (Review). *International Journal of Oncology*, *65*(1). https://doi.org/10.3892/ijo.2024.5661

Zur Hausen, H. (2016). E-101 Reinhard Kurth memorial lecture: Zoonotic origin of some common human cancers and multiple sclerosis? *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *71*.