RESEARCH PAPER

Harmonizing Indian Traditional Medicine with Advanced Cancer Immunotherapy: A Fusion of Ancient Wisdom and Modern Innovation

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ABSTRACT

The convergence of Indian traditional medicine and advanced cancer immunotherapy represents a promising interdisciplinary frontier in oncology. Traditional systems such as Ayurveda and Siddha emphasize holistic healing through herbal formulations, dietary interventions, and lifestyle modifications aimed at restoring immune balance. These approaches align well with contemporary immunotherapeutic strategies, including immune checkpoint inhibitors, CAR-T cell therapy, monoclonal antibodies, and gene-editing technologies. Integrating traditional knowledge with modern immunotherapy could enhance treatment efficacy, minimize adverse effects, and improve patient quality of life. Natural compounds such as curcumin, berberine, and ashwagandha have demonstrated immunomodulatory and anti-cancer properties, showing potential as complementary agents. Furthermore, emerging evidence underscores the pivotal role of the gut microbiome in cancer progression and therapeutic response, with fecal microbiota transplantation (FMT), probiotics, and diet-based interventions showing clinical promise. This review consolidates historical perspectives, therapeutic advances, microbiome-cancer interactions, and the role of bioactive herbal compounds in immunomodulation, highlighting their synergistic potential in shaping next-generation cancer therapies. By bridging ancient wisdom with cutting-edge biomedical innovation, a more personalized, sustainable, and integrative paradigm for cancer care may be realized.

Keywords: Cancer Immunotherapy, Gut Microbiome, Immunomodulation, Herbal Compounds, Integrative Oncology, Traditional Medicine.

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1. Introduction

1.1. Origins and Definition of Cancer

The origins of the term cancer date back more than 2,300 years to the observations of Hippocrates, who described malignant growths as karkinoma, later translated into Latin as cancer. In the 1600s, Robert Hooke's identification of cells in living tissues and Rudolf Virchow's 19th-century proposal that all cells arise from pre-existing cells laid the foundation for modern cellular pathology. Today, cancer is recognized as one of the most formidable global health challenges, ranking as the second leading cause of death worldwide after cardiovascular diseases. It is characterized by uncontrolled cell proliferation, driven by genetic alterations in cell cycle-regulating genes and mutations in key signaling pathways [1]. Despite remarkable advances in diagnosis and treatment, millions of patients continue to succumb to the disease annually.

1.2. Historical Evolution of Cancer Treatments

The journey of cancer therapy has been marked by continuous innovation over the past two centuries. The introduction of general anesthesia in the mid-1800s enabled effective surgical tumor excision. Shortly thereafter, Wilhelm Conrad Röntgen's discovery of X-rays revolutionized oncology by introducing radiation therapy. The mid-20th century saw the advent of chemotherapy, pioneered using nitrogen mustards during World War II, which significantly broadened treatment strategies. More

recent breakthroughs, including immunotherapy and gene therapy, have transformed cancer management, providing precision and long-term survival benefits [2] (Figure 1).

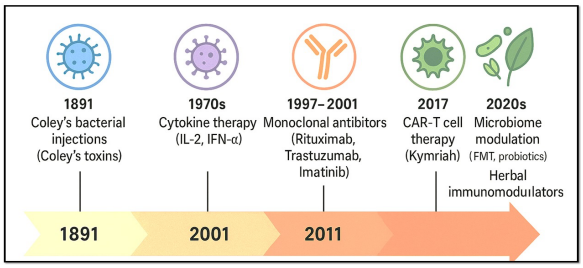

Figure 1: The Evolution of Cancer Immunotherapy: From Coley's Toxins to Precision Immuno-Oncology

Key milestones in the evolution of FDA-approved cancer therapies highlight the progressive shift from nonspecific cytotoxic agents to precision-targeted and immune-based interventions. In 1990, Bacillus Calmette–Guérin (BCG) was approved for non-invasive bladder cancer, marking one of the earliest immunotherapeutic applications. Rituximab, introduced in 1997, became the first monoclonal antibody targeting B-cell lymphomas, ushering in the era of targeted biologics. In 1999, Trastuzumab revolutionized treatment for HER2-positive breast cancer by enabling molecularly guided therapy. The approval of Imatinib in 2001, the first kinase inhibitor, transformed chronic myeloid leukemia (CML) management and validated oncogene-directed drug development. Between 2003 and 2004, Gefitinib and Erlotinib advanced therapy for non–small cell lung cancer (NSCLC), while Bevacizumab emerged as the first anti-angiogenic agent. Sorafenib, approved in 2005, extended targeted therapy to renal cell carcinoma. The advent of CAR-T cell therapy in 2011 marked a paradigm shift in leukemia treatment, demonstrating the power of engineered immunity. In 2014, immune checkpoint inhibitors Pembrolizumab and Nivolumab transformed melanoma care, alongside BRAF-targeted agents Trametinib and Dabrafenib. From 2015 to 2021, the field expanded into preventive oncology with Gardasil 9 (HPV vaccine) and witnessed renewed interest in oncolytic virotherapy with T-VEC and Delytact, underscoring the continued convergence of immunology, genetics, and virotherapy in modern oncology.

1.3. Advances in Antibody and Immunotherapy Development

Antibodies have played a central role in shaping modern immunology and oncology. Ancient practices of variolation in Asia laid the foundation for immune protection, culminating in Edward Jenner's landmark smallpox vaccination in 1796 [3]. Subsequent discoveries, including Emil von Behring and Shibasaburo Kitasato's serum therapy [4], Paul Ehrlich's side chain theory [5], and Ilya Mechnikov's identification of phagocytosis, established the dual framework of humoral and cellular immunity [6,7]. The 20th century marked the molecular revolution in immunology. Structural characterization of antibodies [8], Burnet's clonal selection theory, and Tonegawa's demonstration of V(D)J recombination [9] explained antibody diversity. Technological innovations such as the hybridoma technique enabled the production of monoclonal antibodies, paving the way for therapeutic breakthroughs including Rituximab and Herceptin [10]. By the late 20th century, antibodies evolved into powerful therapeutics, ranging from immune checkpoint inhibitors (ipilimumab, pembrolizumab) [11] to CAR-T cell therapies [12]. The recent introduction of antibody-drug conjugates (ADCs), bispecific antibodies, nanobodies, and mRNA-based technologies [13]. demonstrates the versatility of antibody science in precision oncology. Emerging frontiers now integrate artificial intelligence (AI) and machine learning in antibody design [14], accelerating discovery pipelines and optimizing clinical efficacy.

1.4. Emerging Trends in Cancer Therapy:

1.4.1. Targeted Drug Specialization:

From angiogenesis inhibitors (Lapatinib, Gefitinib, Sorafenib) to metabolic regulators (IDO1, IDH1/2 inhibitors), therapeutic precision is improving [15].

1.4.2. Shift from Small Molecules to Biologics:

Treatments now include small molecules (Imatinib, Neratinib), peptide-based agents (Sandostatin, Lutathera), and advanced cell-based therapies (CAR-T, NK cells, TILs).

1.4.3. Combination Therapies:

Multimodal regimens combining chemotherapy, targeted therapy, and immunotherapy are replacing monotherapy approaches.

1.4.4. Novel Platforms:

Research into neoantigen vaccines, oncolytic viruses, gene therapies, adjuvants, and next-generation photodynamic therapy represents the cutting edge of clinical oncology.

1.5. Challenges in Cancer Therapy:

Despite progress, cancer therapy continues to face major hurdles. Metastasis remains the leading cause of cancer mortality, as malignant cells invade distant tissues, complicating treatment [16,17]. Tumor heterogeneity and frequent recurrences undermine long-term success. Resistance to chemotherapy and

radiotherapy further limits efficacy. Moreover, cancer cells employ mechanisms to evade immune surveillance, weakening immunotherapy responses. Chemotherapy, although widely used, often suffers from poor bioavailability, non-specific toxicity, and pharmacokinetic limitations [18]. Ultimately, the challenge remains to selectively eradicate malignant cells while sparing normal tissues, a goal yet to be fully achieved despite extensive research efforts.

2. The Evolution of Immunotherapy:

Immunotherapy has transformed oncology by offering strategies that harness the body's immune system to recognize and eliminate malignant cells. Unlike conventional therapies such as chemotherapy or radiotherapy, which directly target tumor cells, immunotherapies restore or enhance immune surveillance, leading to durable responses in cancers once considered untreatable. Many of these therapies have been granted accelerated approvals, reflecting their disruptive potential in oncology [19]. The concept of immunotherapy dates back centuries, with early efforts to stimulate immunity against tumors through deliberate infection. A landmark in 1891 came from William Coley, often regarded as the "Father of Immunotherapy," who injected streptococcal bacteria into patients with metastatic sarcomas, leading to tumor regression [20]. Although crude, this provided the first evidence that an activated immune system could control cancer. In the 1950s, Burnet and Thomas proposed the immunosurveillance theory, which posited that the immune system can recognize and eliminate emerging cancer cells by detecting tumor-associated antigens (TAAs). This foundational concept later evolved into the modern framework of cancer immunoediting, encompassing three interrelated phases. The elimination phase involves immune recognition and destruction of transformed cells through coordinated innate and adaptive responses. During the equilibrium phase, a dynamic balance is maintained between immune pressure and tumor adaptation, allowing the selection of less immunogenic variants. In the escape phase, tumor cells acquire mechanisms to evade immune detection and destruction, facilitating uncontrolled proliferation and disease progression. This triphasic model has profoundly influenced the development and optimization of contemporary immunotherapeutic strategies.

2.1. Cytokine Therapy: Early Immune Modulators

Cytokines were among the earliest immune modulators explored for cancer therapy. In 1974, interleukin-2 (IL-2), initially termed "T-cell growth factor", was discovered as a pivotal regulator of T-cell differentiation and immune memory. Preclinical studies in the 1980s demonstrated IL-2's ability to shrink metastatic tumors, leading to FDA approval in 1992 for metastatic renal cell carcinoma. Despite its landmark status, IL-2 therapy was limited by life-threatening toxicities such as capillary leak syndrome, restricting its use to specialized centers. Other cytokines, including interferon-alpha (IFN-α), showed promise but faced similar challenges of toxicity and inconsistent efficacy. Nonetheless, cytokine therapy established the principle that immune signaling molecules could be harnessed against cancer.

2.2. Immune Checkpoint Inhibitors: A Paradigm Shift

One of the most transformative discoveries in oncology has been immune checkpoint inhibition, which reinvigorates T cells suppressed by tumors. The first checkpoint molecule identified was CTLA-4, discovered in 1987 by Pierre Golstein's group [21]. Subsequent work by Jeffrey Bluestone, Peter Linsley, and James Allison revealed its role as a negative regulator of T-cell activation. In 2011, Allison's research led to the approval of ipilimumab, an anti-CTLA-4 antibody, for metastatic melanoma, the first immune checkpoint inhibitor (ICI) in clinical practice [22,23]. A second critical checkpoint was programmed death-1 (PD-1), cloned by Tasuku Honjo in 1992. PD-1 and its ligands PD-L1/PD-L2 suppress T-cell activity in the tumor microenvironment. The development of anti-PD-1 antibodies such as pembrolizumab and nivolumab, and PD-L1 inhibitors including atezolizumab, avelumab, and durvalumab, revolutionized the management of melanoma, NSCLC, renal, bladder, and many other cancers. Today, at least eight ICIs are approved across 18 malignancies. Checkpoint blockade represented a shift from direct tumor cytotoxicity to removing inhibitory brakes on the immune system. However, challenges remain, including resistance mechanisms, variable response rates, and immune-related toxicities. Nevertheless, the pioneering contributions of James Allison and Tasuku Honjo were recognized with the 2018 Nobel Prize in Physiology or Medicine, underscoring the global impact of checkpoint therapy.

2.3. Monoclonal Antibodies: Targeted Immune Therapies

The recognition that tumor cells express specific antigens led to the rise of monoclonal antibodies (mAbs) as precision therapies. The hybridoma technique developed by Köhler and Milstein enabled large-scale production of mAbs, laying the

groundwork for their clinical application. Rituximab, targeting CD20, was FDA-approved in 1997 for non-Hodgkin's lymphoma and remains a cornerstone in B-cell malignancy treatment. Trastuzumab (Herceptin), approved in 1998, revolutionized HER2-positive breast and gastric cancer care, significantly improving survival outcomes. Despite these successes, resistance to mAbs and tumor immune evasion posed challenges. To address this, antibody-drug conjugates (ADCs) were developed, coupling cytotoxic agents to antibodies for enhanced specificity. For example, ado-trastuzumab emtansine (Kadcyla) combines trastuzumab with a chemotherapeutic payload, enabling direct tumor cell killing [24] (Table 1).

Table 1. FDA-Approved Monoclonal Antibodies and Immunotherapeutic Agents in Oncology: Mechanisms, Targets, and Clinical Indications

INN (Generic)	Brand Name	Origin	Primary Target(s)	Oncology Indications (Summary)
Ibritumomab tiuxetan	Zevalin	Murine	CD20	Relapsed/refractory $CD20^+$ follicular NHL; consolidation post-response
Tositumomab / I-131 tositumomab	Bexxar	Murine	CD20	Relapsed/refractory $CD20^+$ NHL
Edrecolomab	Panorex	Murine	EpCAM	Adjuvant colon cancer (historic; withdrawn)
Rituximab	Rituxan / MabThera	Chimeric	CD20	NHL, CLL
Cetuximab	Erbitux	Chimeric	EGFR	mCRC (RAS WT), HNSCC
Brentuximab vedotin	Adcetris	Chimeric	CD30	HL, sALCL, PTCL, CTCL (indication varies)
Dinutuximab	Unituxin	Chimeric	GD2	High-risk neuroblastoma (pediatric)
Isatuximab	Sarclisa	Chimeric	CD38	Multiple myeloma
Nimotuzumab	BIOMAb EGFR (IN)	Humanised	EGFR	HNSCC (India); NPC (China); glioma (Cuba/others)
Trastuzumab	Herceptin	Humanised	HER2	$HER2^+$ breast; gastric/GEJ
Pertuzumab	Perjeta	Humanised	HER2 (dimerization)	$HER2^+$ breast (neo/adjuvant; metastatic)
Bevacizumab	Avastin	Humanised	VEGF-A	CRC, NSCLC, RCC, GBM, cervical, ovarian
Atezolizumab	Tecentriq	Humanised	PD-L1	Urothelial; NSCLC; SCLC (maintenance); HCC (+ bevacizumab); TNBC
Pembrolizumab	Keytruda	Humanised	PD-1	Multiple tumors; MSI-H/TMB-H; heme malignancies
Gemtuzumab ozogamicin	Mylotarg	Humanised	CD33	AML (newly diagnosed & R/R)
Inotuzumab ozogamicin	Besponsa	Humanised	CD22	R/R B-ALL
Polatuzumab vedotin	Polivy	Humanised	CD79b	DLBCL (various settings)
Sacituzumab govitecan	Trodelvy	Humanised	TROP-2	mTNBC; $HR^+/HER2^-$ breast; urothelial (US

				withdrawn AA)
Trastuzumab emtansine	Kadcyla	Humanised	HER2	HER2+ breast (adjuvant; metastatic)
Trastuzumab deruxtecan	Enhertu	Humanised	HER2 / HER2-low	Breast; gastric; NSCLC (HER2 mut)
Mirvetuximab soravtansine	Elahere	Humanised	FOLR1	Platinum-resistant ovarian/fallopian/peritoneal
Dostarlimab	Jemperli	Humanised	PD-1	dMMR/MSI-H endometrial; dMMR solid tumors
Tisotumab vedotin	Tivdak	Humanised	Tissue factor (TF)	Recurrent/metastatic cervical cancer
Loncastuximab tesirine	Zynlonta	Humanised	CD19	R/R DLBCL
Mogamulizumab	Poteligeo	Humanised	CCR4	CTCL (MF/SS)
Naxitamab gqgk	Danyelza	Humanised	GD2	R/R high-risk neuroblastoma
Tafasitamab	Monjuvi / MINJUVI	Humanised	CD19	R/R DLBCL (+ lenalidomide)
Zolbetuximab	Vyloy	Chimeric/ Humanised	Claudin 18.2	Gastric/GEJ adenocarcinoma (CLDN18.2+)
Panitumumab	Vectibix	Human	EGFR	mCRC (RAS WT)
Nivolumab	Opdivo	Human	PD-1	Multiple solid tumors & heme malignancies
Ipilimumab	Yervoy	Human	CTLA-4	Melanoma; RCC (combo); MSI-H CRC; others
Avelumab	Bavencio	Human	PD-L1	Merkel cell; urothelial maintenance; RCC (combo)
Durvalumab	Imfinzi	Human	PD-L1	NSCLC (stage III post-CRT); SCLC; BTC; HCC (+ tremelimumab)
Cemiplimab	Libtayo	Human	PD-1	CSCC; BCC; NSCLC (PD-L1 high)
Ramucirumab	Cyramza	Human	VEGFR-2	Gastric/GEJ; NSCLC; HCC; CRC
Necitumumab	Portrazza	Human	EGFR	Sq NSCLC (+ chemo)
Daratumumab	Darzalex / Faspro	Human	CD38	Multiple myeloma (various lines)
Amivantamab	Rybrevant	Human	EGFR, MET	NSCLC (EGFR exon20ins; + chemo for common EGFR mut)
Blinatumomab	Blincyto	Murine (BiTE scFv)	CD19, CD3	B-ALL (adult/pediatric; MRD+ & R/R)
Mosunetuzumab	Lunsumio	Humanised	CD20, CD3	R/R follicular lymphoma
Glofitamab	Columvi	Humanised	CD20, CD3	R/R DLBCL / LBCL
Epcoritamab	Epkinly / Tepkinly	Humanised	CD20, CD3	R/R DLBCL
Teclistamab	Tecvayli	Humanised	BCMA	R/R multiple

mab	ayli	d	A, CD3	myeloma
Talquetamab	Talvey	Humanised	GPRC5D, CD3	R/R multiple myeloma
Elranatamab	Elrexfio	Humanised	BCMA, CD3	R/R multiple myeloma
Enfortumab vedotin	Padcev	Human	Nectin-4	Urothelial carcinoma
Belantamab mafodotin	Blenrep	Humanised	BCMA	Multiple myeloma (combo labels evolving)
Datopotamab deruxtecan	Datroway (US) / Dato DXd	Humanised	TROP-2	$HR^+/HER2^-$ breast; NSCLC (US 2025)
Patritumab deruxtecan	HER3 DXd	Human	HER3	EGFR-mut NSCLC post-TKI & chemo
Ofatumumab	Arzerra	Human	CD20	CLL (historic)
Obinutuzumab	Gazyva / Gazyvaro	Humanised	CD20	CLL; FL (incl. maintenance)
Relatlimab + Nivolumab (fixed)	Opdualag	Human (relatlimab)	LAG-3, PD-1	Unresectable/metastatic melanoma (≥12 y)
Tremelimumab	Imjudo	Human		

2.5. CAR-T Cell Therapy: Engineering T Cells for Precision

Chimeric antigen receptor T-cell (CAR-T) therapy represents one of the most transformative advances in cancer immunotherapy. Developed in the 1990s by Eshhar and colleagues, CAR-T technology involves genetically engineering a patient's own T cells to express synthetic receptors that specifically recognize tumor-associated antigens [25]. This reprogramming enables T cells to bypass conventional antigen presentation pathways and directly attack malignant cells.

The clinical breakthrough came in 2017 with the FDA approval of tisagenlecleucel (Kymriah), the first CAR-T therapy, for relapsed or refractory acute lymphoblastic leukemia. Since then, multiple CAR-T products have been approved for B-cell malignancies, demonstrating unprecedented complete response rates and durable remissions in patients with limited therapeutic options.

Despite these successes, the translation of CAR-T therapy to solid tumors remains challenging. Barriers include tumor heterogeneity, the immunosuppressive tumor microenvironment, and limited trafficking of CAR-T cells to solid tumor sites. Current research efforts are exploring novel targets such as HER2 in breast cancer and PSMA in prostate cancer, alongside strategies like armored CAR-T cells, dual-targeting constructs, and microenvironment modulation. These innovations aim to extend the remarkable efficacy of CAR-T therapy beyond hematologic cancers.

2.6. The Future of Cancer Immunotherapy: Toward Personalized Integration

The future of immunotherapy is increasingly defined by diversification, personalization, and synergistic integration of multiple modalities. Several innovative strategies are currently transforming the therapeutic landscape. Neoantigen vaccines, which target patient-specific tumor mutations, are being actively investigated in clinical trials and offer the promise of generating highly individualized and durable immune responses. Bispecific antibodies represent another frontier, engineered to simultaneously bind immune effector cells and tumor antigens, thereby enhancing precision and minimizing therapeutic resistance. Oncolytic viruses are designed to selectively infect and lyse malignant cells while concurrently stimulating systemic antitumor immunity. Combination therapies, integrating checkpoint inhibitors, monoclonal antibodies, cytokines, and CAR-T cells, have demonstrated superior efficacy compared to monotherapies by exploiting complementary and synergistic mechanisms. Looking ahead, the field is moving toward deeply personalized medicine, where genomic, proteomic, and microbiome profiling inform rational therapeutic selection. Concurrently, advances in artificial intelligence and computational biology are accelerating the discovery of new immunologic targets and optimizing treatment design. Collectively, these innovations are poised to transform cancer

immunotherapy into a more precise, durable, and patient-centered paradigm.

3. Gut Microbiota in Cancer

The gut microbiota influences every stage of carcinogenesis, from initiation and promotion to progression and therapeutic response, through inflammation, genotoxic metabolites, immune modulation, and direct tumor, microbe interactions. Distinct microbial signatures are consistently observed between healthy individuals and patients with cancer, and even across cancer subtypes, positioning the microbiome as both a mechanistic driver and a potential biomarker of disease (Figure 2).

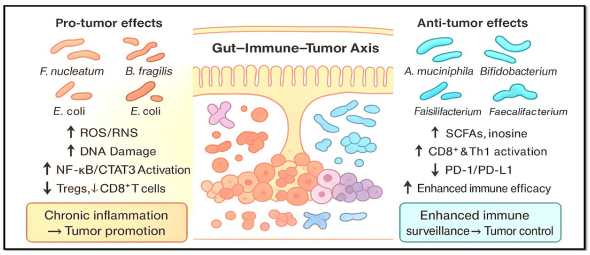

Figure 2: The Gut Microbiota–Immune System Axis in Cancer and Immunotherapy

3.1 Microbial Pathways of Carcinogenesis and Tumor Promotion

3.1.1. Role of Chronic Inflammation

Inflammation can both restrain and promote tumor growth. Within the tumor microenvironment, cytokines and reactive oxygen/nitrogen species increase mutation rates, compromise DNA repair, and fuel genomic instability, features now recognized as hallmarks of cancer [26]. Microbes can initiate tumorigenesis by provoking tumor-promoting inflammation or by persisting within inflamed niches of existing tumors. In colorectal cancer (CRC), poorer outcomes correlate with enrichment of *Fusobacterium nucleatum*, upregulation of TNF-α, β-catenin, and NF-κB, and a myeloid shift from M1 to M2 phenotypes; conversely, *Faecalibacterium prausnitzii* associates with improved survival and lower NF-κB/β-catenin signaling and MMP9 expression [27].

Innate immunity is central to how commensals elicit inflammation. Toll-like receptors (TLRs) detect pathogen-associated molecular patterns and help maintain intestinal homeostasis; dysregulation can drive chronic inflammation [28]. TLR4 overexpression in ulcerative colitis and CAC models promotes colon tumorigenesis via EGFR activation, while MyD88 signaling is critical for spontaneous intestinal tumor growth. Barrier-disrupting microbial toxins further increase antigen translocation and local inflammation. Persistent NF-κB activation and perturbation of Wnt/β-catenin signaling synergize to accelerate tumor progression.

Inflammasomes (NLRs + ASC + pro-caspase-1) sense PAMPs/DAMPs and activate caspase-1 to mature IL-1β/IL-18 [29,30]. Proper inflammasome function preserves microbial balance, whereas component deficiencies cause dysbiosis and inflammation-driven malignancy (AOM/DSS models). NOD2 shapes microbial composition; its loss heightens risk for colitis and colitis-associated cancer, and the dysbiotic state is transmissible by fecal transfer [31].

Adaptive immunity also integrates microbial cues. Microbes that induce Th17 cells (e.g., segmented filamentous bacteria; enterotoxigenic Bacteroides fragilis) can sustain inflammation and elevate cancer risk, though therapy-induced Th17 responses (e.g., with cyclophosphamide) may be anti-tumor depending on context. Tregs counter inflammation-driven tumorigenesis in an IL-10–dependent manner; *B. fragilis* polysaccharide A promotes IL-10 in CD4 T cells, dampening IL-17–mediated pathology.

3.1.2 Carcinogenic Toxins and Metabolites:

Beyond inflammation, microbial products can directly drive cancer. *Helicobacter pylori* CagA promotes gastric carcinogenesis by destabilizing genome integrity and perturbing SHP2, E-cadherin, and PAR1 signaling. Enterotoxigenic *B. fragilis* (BFT) induces epithelial SMO, elevates ROS and DNA breaks, and cleaves E-cadherin to mobilize β-catenin and c-MYC. Diet-linked metabolites from dysbiosis (N-nitroso compounds, ammonia, H_2S, secondary bile acids) provoke inflammation and DNA damage; deoxycholic acid promotes ROS/RNS, mutagenesis, apoptosis escape, and pro-proliferative β-catenin signaling. Conversely, short-chain fatty acids (butyrate, propionate, acetate) can be anti-inflammatory and anti-tumor. Microbial ligands sensed by PRRs (TLRs/NLRs) activate NF-κB/STAT3 cascades, shaping APC and T-cell responses in mesenteric lymph nodes [32]. When these pathways are overactivated, antitumor immunity is suppressed and proliferation/metastasis are enhanced.

The Gut Microbiome and Cancer: Case Evidence

3.1.3. Colorectal Cancer (CRC)

CRC incidence has risen among young adults, with strong mechanistic links to specific bacteria. *Escherichia coli*, *Enterococcus faecalis*, *F. nucleatum* [33], and *Bacteroides fragilis* contribute to tumorigenesis. Enterotoxigenic *B. fragilis* (BFT) activates STAT3 and Th17 responses, driving colonic tumors; levels are higher in CRC than controls [34,35]. *F. nucleatum* adheres to CRC cells, activates

TLR4 signaling, promotes inflammation, and dampens antitumor immunity [36,37]. *E. faecalis* releases superoxide/H_2O_2 causing DNA damage; CNF1 activity is linked to proliferation and invasion. pks+ E. coli generates colibactin, inducing double-strand breaks and accelerating tumorigenesis [38]. CRC microbiota typically shows decreased Roseburia and increased Bacteroides, Escherichia, Fusobacterium, and Porphyromonas [39,40], with enrichment of Prevotella, Peptostreptococcus, Parvimonas, and Porphyromonas; *Peptostreptococcus anaerobius* promotes carcinogenesis via TLR2/TLR4 activation [41,42]. *Clostridioides difficile* overabundance is also reported.

3.1.4. Microbiome as a Biomarker for CRC

Composite microbial panels enable early detection. Seven-species models including *B. fragilis*, *F. nucleatum*, *Parvimonas micra*, *Porphyromonas asaccharolytica*, *Prevotella intermedia*, *Thermanaerovibrio acidaminovorans*, and *Alistipes finegoldii* achieved AUC ≈ 0.80–0.88 with clinical data [43,44]. SNV-based classifiers leveraging 22 bacterial variants (notably from *Eubacterium rectale* and *F. nucleatum*) reached AUCs of ~73–88% and retained specificity across metabolic comorbidities [45,46].

3.1.5. Esophageal Cancer:

Esophageal cancer associates with Gram-negative, LPS-rich communities that elevate iNOS, linking dysbiosis to GERD, a key risk factor [47]. Patients show reduced Bacteroidetes and increased Firmicutes/Actinobacteria; fecal Bacteroidetes, Fusobacteria, and Spirochaetes are also diminished [48].

3.5. Liver Cancer:

Barrier defects permit microbial LPS to induce CXCL1 via TLR4 in hepatocytes, recruiting CXCR2+ PMN-MDSCs and fostering immunosuppression that supports HCC progression [49]. HCC fecal profiles show enrichment of Streptococcus, Lactobacillus, Prevotella 9, Faecalibacterium, and Bacteroides, with reductions in Akkermansia, Subdoligranulum, Prevotella 2, and Faecalibacterium; LPS-producers (e.g., *Klebsiella*) increase while butyrate producers (Ruminococcus) decrease [50]. GelE+ E. faecalis augments permeability, elevates plasma LPS, activates TLR4–MYD88, and drives hepatocyte proliferation [51].

3.1.6. Breast Cancer

Menopause-related hormonal shifts coincide with gut microbiota changes [52]. Premenopausal BC shows higher Enterobacteriaceae, Lactobacilli, and aerobic streptococci, and increased Bacteroides/Clostridia; postmenopausal BC shows decreased Bacteroides and increased Clostridiales [53]. Species-level changes include reduced Roseburia inulinivorans/Eubacterium eligens and elevations in *Acinetobacter radioresistens*, *E. coli*, *Salmonella enterica*, and *F. nucleatum.* Estrogen microbiome interactions likely contribute to risk. Overall patterns support microbiota as biomarkers and therapeutic targets [54].

3.1.7. Hematological Diseases

In hematologic malignancies, microbiota studies are complicated by chemotherapy, immunotherapy, and prophylactic antibiotics, all which remodel gut communities and confound disease-linked signals [55].

3.1.8. Lymphoma in Ataxia-Telangiectasia (A-T):

A-T models reveal microbiota-modulated lymphoma risk. *Lactobacillus johnsonii* abundance correlated with resistance; oral supplementation lowered inflammation and genotoxicity. Mice in cleaner environments lived longer with fewer lymphomas, coincident with reduced systemic inflammation (lower leukocytes and cytokine activation) [56].

3.1.9. AYA Hodgkin Lymphoma:

Adolescent/young adult HL survivors reported fewer early fecal–oral exposures than controls, suggesting altered microbial education and increased HL risk [57,58]. AYAHL is characterized by reduced Th1 and elevated Th2 responses; normal maturation from Th2- to Th1-dominance may be incomplete, with higher Th2 cytokines/IgE and lower cytotoxic T/NK cells [59,60]. Twins studies show fewer rare taxa in survivors, though causality (predisposition vs disease vs treatment) remains unsettled. Multiple oncogenic pathogens (EBV, HHV-8, HTLV-1, *H. pylori*) also contribute to lymphomagenesis [61].

3.1.10. Tumor-Resident Microbiomes

Microbes inhabit diverse tumors and can either promote or restrain cancer. They induce DNA damage, oncogenic signaling, chronic inflammation, complement activation, and metastasis; alternatively, some microbes enhance antitumor immunity and improve responses to therapy, influencing survival. Pan-cancer profiling demonstrates tumor-type–specific microbial communities across colorectal, lung, breast, and other cancers [62].

3.1.11. Tumor Microbiota in CRC:

CRC tissues are dominated by Firmicutes and Bacteroidetes. Abundance of *F. nucleatum* and *Solobacterium moorei* increases from early to late stages; ETBF and E. coli (especially pks & strains)

are enriched and associate with invasiveness/multiplicity [63,64].

3.1.12. Lung Cancer:

Contrary to the "sterile lung" notion, both healthy and malignant lungs harbor microbiota [65,66]. Lung tumors display distinct profiles: E. coli, Haemophilus influenzae, Enterobacter, Staphylococcus, and elevated Firmicutes/TM7 (e.g., Veillonella, Megasphaera). Other signatures include Streptococcus, Acinetobacter, Thermus, *Granulicatella adiacens*, Enterococcus, Prevotella, Rothia, Brevundimonas, Propionibacterium, and Legionella; Actinobacteria/Firmicutes are often increased versus controls [67,68]. Microbiota varies by histology, site, stage, and assay; Thermus associates with advanced disease, while qPCR confirms shifts in Neisseria, Capnocytophaga, Veillonella; Klebsiella, Comamonas, Rhodoferax, Acidovorax, and Polaromonas recur in small-cell carcinoma [69].

3.1.13. Pancreatic Cancer

PDAC exhibits distinctive phylum-level composition: Proteobacteria (~45%), Bacteroidetes (~31%), Firmicutes (~22%), Actinobacteria (~1%). Proteobacteria, especially Gammaproteobacteria (present in ~76% of PDAC), induce T-cell anergy via TLR-dependent pathways, accelerating disease [70]. Genera include Pseudomonas and Elizabethkingia; Bifidobacterium pseudolongum and F. nucleatum are also detected [71]. Longer-survivor tumors are enriched for Pseudoxanthomonas, Streptomyces, and Saccharopolyspora, whereas Bacillus clausii associates with shorter survival [72].

3.1.14. Cholangiocarcinoma:

Across 266 identified species, Clostridiales, Sphingomonadales, Pseudomonadales, Burkholderiales, Bacillales, and Xanthomonadales predominate. Intrahepatic cholangiocarcinoma shows increased H. pylori, H. hepaticus, and H. bilis. Gram-negative–driven TLR4–CXCL1 signaling promotes CXCR2+ PMN-MDSC accumulation, creating an immunosuppressive niche that supports liver tumor development [73].

3.1.15. Breast Tumor Microbiota:

Breast tumors harbor Actinobacteria, Proteobacteria, Bacteroidetes, Firmicutes, and Verrucomicrobia. Firmicutes/Actinobacteria/Proteobacteria are often elevated; *Mycobacterium phlei* and *M. fortuitum* have been identified in tumor tissues. Subtype-specific patterns include enrichment of Proteobacteria and Actinomyces; *Methylobacterium radiotolerans* increases while *Sphingomonas yanoikuyae* decreases [74,75]. *F. nucleatum* accumulates in malignant tissues and promotes aggressiveness via chemokine pathways (e.g., CCL20–Treg recruitment). *B. fragilis* has been detected in tumors. Other enriched taxa include Comamonadaceae, Bacteroidetes, Enterobacteriaceae, Bacillus, Staphylococcus, Propionicimonas, and families Methylobacteriaceae, Caulobacteraceae, Nocardioidaceae, Rhodobacteraceae, and Micrococcaceae; Agrococcus and Bacteroidaceae may be reduced [76].

4. Cancer Immunotherapy:

4.1. The Gut Microbiome in Tumor Immunotherapy:

Tumor progression often reflects failures in immune regulation and active immune evasion by cancer cells (e.g., antigen loss, immunosuppressive TME). Immunotherapy restores or augments antitumor immunity and has improved survival and quality of life in patients refractory to chemo-radiotherapy, yet clinical responses vary widely [77]. Multiple studies link baseline stool microbiome composition to immunotherapy efficacy, implicating intestinal bacteria as modulators of treatment outcome. While most evidence remains preclinical, translating these insights into routine oncology requires standardized cohorts, unified endpoints, and mechanistic clarity [78,79].

4.2. Immune Checkpoint Blockade (ICB)

ICB targets inhibitory receptors, primarily CTLA-4 and PD-1/PD-L1, to release brakes on T cells and trigger antitumor responses [80,81]. Additional checkpoints (LAG3, TIGIT, TIM3, CD39, CD47, CD73) are under active evaluation. Despite transformative impact, many patients derive no durable benefit; even in melanoma, >60–70% fail to respond to anti-PD-1 and ~20–30% eventually relapse [82,83]. Cross-cohort FMT experiments show that transferring feces from human ICB responders or non-responders into germ-free/antibiotic-treated tumor-bearing mice recapitulates human outcomes, establishing a causal role for gut microbes in ICB efficacy [84,85]. Sequencing, culture-based studies, and controlled supplementation point to shared microbial functions (e.g., SCFA production) rather than a single universal "beneficial" taxon as key determinants [86]. Microbial-associated molecular pattern (MAMP) and pathogen-associated molecular pattern (PAMP) signaling, mediated by components such as exopolysaccharides and surface proteins, plays a pivotal role in priming both innate and adaptive immune responses, thereby influencing antitumor immunity. Additionally, microbial

metabolites including short-chain fatty acids (SCFAs), inosine, peptidoglycan fragments, trimethylamine N-oxide (TMAO), and various neurotransmitters can enter systemic circulation and modulate the tumor microenvironment (TME), often biasing immune activity toward tumor control. In patients with non–small cell lung cancer (NSCLC) treated with nivolumab, metabolic profiling revealed that elevated levels of 2-pentanone and tridecane correlated with early disease progression, whereas increased SCFAs, lysine, and nicotinic acid were associated with durable clinical benefit. Moreover, modulation of the gut microbiota may help mitigate immune-related adverse events (irAEs) induced by CTLA-4 and PD-1 monoclonal antibodies. However, due to significant interstudy variability, larger and harmonized multi-omic datasets are essential to define robust microbial consortia that can be rationally exploited to enhance immunotherapy outcomes in clinical practice.

4.3. Adoptive T-Cell Therapy (ACT):

The efficacy of immune checkpoint blockade (ICB) relies on the presence of pre-existing tumor-specific T cells within the tumor microenvironment; consequently, "cold" tumors with limited immune infiltration often exhibit poor responses. Adoptive cell therapy (ACT) addresses this limitation by isolating tumor-reactive T cells, such as tumor-infiltrating lymphocytes (TILs) or cytotoxic T lymphocytes (CTLs), from tumor tissue or peripheral blood, expanding or genetically engineering them ex vivo, and reinfusing them into the patient to mediate targeted cytotoxicity. Chimeric antigen receptor (CAR) T-cell therapy further circumvents major histocompatibility complex (MHC) restrictions by equipping T cells with synthetic receptors that directly recognize tumor antigens, achieving remarkable success in hematologic malignancies and certain cases of metastatic melanoma. Emerging evidence also implicates the gut microbiome in modulating ACT and CAR-T outcomes: prior exposure to broad-spectrum antibiotics correlates with reduced survival and increased neurotoxicity following CD19-targeted CAR-T therapy, whereas enrichment of bacterial genera such as Ruminococcus, Bacteroides, and Faecalibacterium is associated with improved therapeutic responses. These findings suggest that microbiota-conscious management before and during CAR-T therapy could optimize both efficacy and safety [87].

4.4. Microbiome and Immunotherapy-Related Toxicity

ICB induces irAEs whose spectra differ by target (e.g., anti-CTLA-4: colitis/hypophysitis; anti-PD-1: thyroiditis/pneumonitis). In melanoma, baseline Bacteroides intestinalis and Intestinibacter bartlettii associated with higher irAE rates and intestinal IL-1β, whereas B. dorei/B. vulgatus linked to fewer irAEs in another cohort—differences likely reflect regimen, functionally redundant taxa, and geography. In neoadjuvant ICB, Ruminococcaceae and Akkermansia muciniphila correlated with reduced efficacy but more severe irAEs across Australian/Netherlands cohorts. Systemic CRP also tracks severe irAEs. With immune-agonist antibodies (anti-CD40, anti-CD137), germ-free or antibiotic-treated mice showed attenuated cytokine-release syndrome, hepatotoxicity, and colitis without losing antitumor efficacy, highlighting microbial contributions to toxicity [88,89]. Similarly, after CD19 CAR-T, antecedent antibiotics were linked to increased neurotoxicity, underscoring the intertwined nature of efficacy and toxicity with gut ecology [90,91].

4.5. Strategies to Modulate the Microbiome:

Because the environment and diet exert profound influences on the composition and function of the gut microbiome, therapeutic modulation of microbial communities is being actively explored as a strategy to enhance the efficacy of immunotherapy. Approaches under investigation include fecal microbiota transplantation (FMT), administration of defined probiotics, and the use of prebiotics or targeted dietary interventions to favor beneficial microbial populations. More recently, rationally designed microbial consortia based on mechanistic insights into host–microbe interactions have emerged as a promising avenue. Although early studies demonstrate the feasibility and potential of these strategies, the development of durable and standardized clinical protocols remains an ongoing challenge [92].

4.6. Fecal Microbiota Transplantation (FMT)

FMT is established for recurrent C. difficile and is now being piloted to enhance ICB. In mice, stool from ICB responders increases antitumor immunity versus non-responder stool [93]. Two phase I trials in metastatic melanoma showed that FMT + anti-PD-1 induced clinical benefit in subsets of patients, with increased $CD8^+$ T-cell activation, favorable transcriptional reprogramming, and responder-like microbiome shifts [94]. Challenges include donor–recipient matching, undefined fecal components, and safety/standardization; thus, FMT is best viewed as a

bridge toward defined next-generation biotherapeutics.

4.7. Probiotics as Adjuncts

Although regulated as supplements (with variable quality), specific strains show promise. In NSCLC, Bifidobacterium bifidum enrichment associated with response; supplementation enhanced oxaliplatin or anti-PD-1 efficacy in models. B. pseudolongum (inosine-producing) activates T-cell pathways and augments anti-tumor immunity in CRC models; Lactobacillus and Streptococcus thermophilus have shown synergism with immunotherapy preclinically. Moving forward requires GMP-grade manufacturing, mechanistic selection of strains, and rigorous trials [95].

4.8. Antibiotics and Treatment Outcomes

Across lymphoma (cisplatin) and CLL (cyclophosphamide) cohorts (CML8, Cologne neutropenia), anti-Gram-positive antibiotics correlated with lower ORR, earlier progression, and independently shorter PFS/OS among 122 lymphoma and 800 CLL patients. Mouse models confirmed that antibiotics can blunt the efficacy of cytotoxics [96]. These data argue for antibiotic stewardship during cancer therapy whenever clinically safe.

4.9. Commensals and Multiple Myeloma (MM)

Commensals drive Th17 differentiation (IL-17), shaping inflammation relevant to MM. In MM-prone mice, Prevotella heparinolytica induced Th17 cells that trafficked to bone marrow and accelerated tumorigenesis; it also promoted eosinophil-mediated inflammation. Clinically, Eubacterium spp. were associated with reduced relapse after allo-HSCT, suggesting protective roles for select commensals [97].

5. Immunomodulatory Effects of Herbal Products:

Harnessing immune modulation is central to cancer therapy, and bioactive compounds derived from medicinal plants have shown considerable promise in this domain. These natural agents influence tumor progression by reshaping the tumor microenvironment (TME) and regulating immune cell populations such as T cells, macrophages, dendritic cells (DCs), mast cells, and natural killer (NK) cells. They also modulate key signaling pathways and immune checkpoints, thereby enhancing antitumor responses while minimizing resistance and toxicity [98].

5.1. Mechanisms of Action

5.1.1. Regulation of T Cells and Checkpoints

Natural products modulate T-cell activity by suppressing immunosuppressive Tregs and enhancing cytotoxic $CD8^+$ T-cell responses. Curcumin converts Tregs into Th1 effector cells, downregulates PD-L1, reduces MDSCs, and enhances $CD8^+$ T-cell cytotoxicity in colorectal and lung cancers. It also suppresses TGF-β, IL-10, and CTLA-4, alleviating immune suppression [99]. In combination with anti-PD-1 therapy, curcumin augments checkpoint blockade in colorectal and liver cancers [100].

Berberine suppresses PD-L1 in NSCLC by promoting its degradation via the ubiquitin–proteasome pathway, reduces Tregs and MDSCs, and enhances tumor-infiltrating T-cell activity. Its antitumor effects are abrogated in T-cell-deficient models, indicating T-cell–dependent activity. Resveratrol amplifies Th1 immunity, strengthens $CD8^+$ T-cell responses, and decreases PD-1 expression. It also interferes with PD-L1 glycosylation, enhancing immune-mediated tumor clearance [101]. Apigenin regulates T-cell and DC functions in breast, lung, pancreatic cancers, and melanoma. It suppresses IFN-γ–induced PD-L1 via STAT1 inhibition, enhances $CD4^+$/$CD8^+$ infiltration, and synergizes with DNA vaccines to boost $CD8^+$ memory responses [102].

5.1.2. Induction of Immunogenic Cell Death

Many herbal compounds trigger apoptotic mechanisms that release tumor antigens and danger-associated signals, activating both innate and adaptive immunity. This promotes antigen presentation, immune priming, and durable antitumor surveillance.

5.1.3. Modulation of Key Signaling Pathways

Natural agents regulate oncogenic and inflammatory cascades, including NF-κB, PI3K/Akt, MAPK, and JAK/STAT, thereby disrupting tumor-driven immune evasion. Such regulation not only strengthens host antitumor responses but also sensitizes tumors to standard therapies [103].

5.1.4. Classes of Active Compounds:

Polyphenols such as curcumin, resveratrol, epigallocatechin gallate (EGCG), and gallic acid exhibit potent antioxidant and anti-inflammatory properties that modulate multiple cellular signaling pathways, contributing to their therapeutic potential against cancer and neurodegenerative diseases. Terpenoids, including paclitaxel, artemisinin, and β-elemene, are known for their cytotoxic and antiproliferative effects, often targeting cell cycle regulation and apoptosis in malignant cells. Polysaccharides such as lentinan and β-glucans enhance immune responses by activating macrophages, natural killer cells, and cytokine production. Other bioactive compounds like ginsenosides, silibinin, triptolide, digoxin, and bufalin exert diverse pharmacological effects, including

anticancer, hepatoprotective, and cardiotonic actions, through modulation of cellular and molecular mechanisms. Each class exhibits immunomodulatory activity by regulating immune checkpoints, promoting antigen presentation, or remodeling the TME. For example, silibinin downregulates PD-L1 by targeting HIF-1α and STAT5 in nasopharyngeal carcinoma, while β-glucans and ginsenosides enhance macrophage and NK cell activity.

5.2. Therapeutic Potential

Compared to monoclonal antibody therapies, herbal compounds typically show lower toxicity and fewer adverse effects, making them attractive as adjuncts. Their pleiotropic activity, targeting multiple pathways simultaneously, offers advantages in reducing resistance and improving chemotherapy sensitivity. Moreover, by influencing both innate and adaptive immunity, these agents create a TME more conducive to long-term tumor suppression (Figure 3).

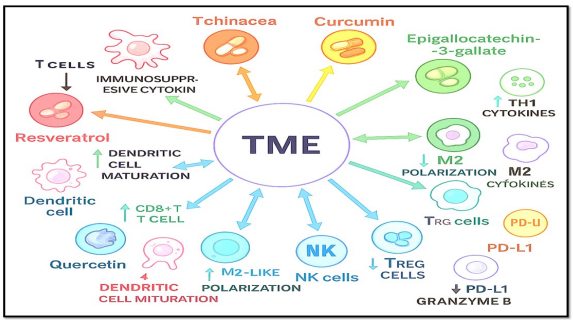

Figure 3: Immunomodulatory Effects of Herbal Compounds on the Tumor Microenvironment

Conclusion:

Over the past century, cancer treatment has progressed from basic surgical interventions and radiotherapy to sophisticated targeted drugs and immunotherapies. Landmark discoveries such as X-rays, early chemotherapy, tyrosine kinase inhibitors, monoclonal antibodies, and more recently CAR-T cell therapy, have significantly advanced patient care. Yet, clinical challenges, including tumor heterogeneity, metastasis, recurrence, and therapeutic resistance, continue to limit long-term success. Recent insights reveal that the gut microbiome plays a pivotal role in shaping cancer development, progression, and treatment outcomes. Specific microbes and their metabolites can foster tumor growth by promoting chronic inflammation and genomic instability, while others enhance immune surveillance and responsiveness to therapy. Variations in microbial composition have been closely linked to patient responses to immune checkpoint inhibitors, adoptive T-cell therapy, and CAR-T cells. Importantly, interventions such as fecal microbiota transplantation (FMT), probiotics, and dietary modulation show promise in enhancing immunotherapy efficacy and mitigating immune-related toxicities. Taken together, these findings highlight the growing importance of integrating microbiome science with modern immunotherapy. By combining conventional anticancer agents with microbiome-targeted strategies, and leveraging personalized microbial profiling, oncology is moving toward a future of more precise, durable, and patient-centered treatments.

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Figure legends

Figure 1: The Evolution of Cancer Immunotherapy: From Coley's Toxins to Precision Immuno-Oncology

Figure 2: The Gut Microbiota–Immune System Axis in Cancer and Immunotherapy

Figure 3: Immunomodulatory Effects of Herbal Compounds on the Tumor Microenvironment