REVIEW

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Chronic Infections as Catalysts for Melanoma Aggressiveness: Insights into Tumour Microenvironment Modulation

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Abstract

Background: Cutaneous melanoma is a highly aggressive skin cancer known for its metastatic potential and resistance to conventional therapies. While genetic and environmental factors are well-recognized in melanoma progression, the impact of chronic microbial infections is not fully understood. Recent studies suggest microbial pathogens interact with the tumour microenvironment, facilitating immune evasion, epithelial-mesenchymal transition (EMT), and therapy resistance. This study aims to explore how chronic infections contribute to melanoma aggressiveness and assess the potential of antimicrobial peptides (AMPs) as a new therapeutic approach. **Methods:** A systematic review was conducted according to PRISMA 2020 guidelines, utilising academic databases (PubMed, Scopus, Web of Science, and Google Scholar) from 2020 to 2025. Peer-reviewed studies were screened to identify microbial species linked to melanoma, antimicrobial resistance (AMR), and the effectiveness of AMPs. Data on cytokines, immune pathways, and bioinformatics approaches to AMP design were synthesized. **Results:** The review revealed that pathogens such as Staphylococcus aureus, Pseudomonas aeruginosa, and Candida tropicalis exacerbate melanoma progression by inducing chronic inflammation, promoting pro-inflammatory cytokines (IL-6, TNF-α), and enhancing EMT, which aids tumour invasion and metastasis. AMR complicates treatment, particularly in immunocompromised patients. AMPs were identified as promising agents due to their dual action: antimicrobial activity and immunomodulation. Advances in bioinformatics and AI have facilitated the rational design of AMPs with improved specificity and reduced cytotoxicity, suggesting potential synergy with immune checkpoint inhibitors and targeted therapies. **Conclusion:** Chronic microbial infections significantly influence melanoma aggressiveness and treatment resistance. AMPs offer a promising, multifunctional therapeutic approach, addressing infection control and tumour microenvironment modulation. Combining AMPs with current immunotherapies may enhance melanoma management. Further research and clinical trials are needed to validate and optimise AMP-based treatments for personalised care.

Keywords: Melanoma progression- Antimicrobial peptides (AMPs)- Chronic infections

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Introduction

Cancer is one of the leading causes of death worldwide, significantly impacting life expectancy and posing a severe challenge to global public health. In 2020, 19.3 million new cancer cases were reported, resulting in 10 million deaths, figures that highlight the devastating impact of this multifactorial disease [1, 2]. Besides its high incidence, cancer imposes a substantial economic and social burden, affecting patients, families, and healthcare systems comprehensively [2, 3]. The origin and development of cancer involve complex interactions among genetic, environmental, and lifestyle factors, contributing to the clinical heterogeneity observed across different tumour types1 [4-6]. Among various cancer types, skin cancers hold a prominent position as the most frequently diagnosed globally [7, 8]. The clinical and epidemiological characteristics of melanoma and non-melanoma skin cancer (NMSC) are strikingly different [3, 7-9]. Most diagnoses are because of NMSC, which typically shows slow growth, low metastatic potential, and an approximately 5.31% mortality rate [3,8,10]. Conversely, melanoma, which represents only 3% of skin cancer diagnoses, is highly aggressive, with a greater propensity for metastasis and elevated lethality, accounting for 75% of deaths attributed to skin cancer

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[2,3,10,11-15].

There are four primary stages of melanoma, each representing the progression of the disease [12,14-19]. Stage 0, also referred to as melanoma in situ, indicates that the tumor is confined to the epidermis [15,16]. Stage I is distinguished by cancer localized within the superficial dermis [15,17]. Stage II is characterized by a thicker tumor that continues to be localized. Stages III and IV pertain to lymph node involvement and metastasis to distant organs, respectively [18-21]. This classification is directly correlated with survival rates, which exhibit a sharp decline from 99% in stage 0 to merely 27% in stage IV, thereby underscoring the significance of early diagnosis for effective treatment [2-4,15, 21-23]. Recent studies have indicated that external factors, such as microbial infections, significantly influence melanoma progression [22, 24, 25]. The interaction between pathogens and the tumor microenvironment contributes to the complexity of the disease, thereby rendering diagnosis and treatment more arduous [26-31]. Bacteria, including Staphylococcus aureus, Pseudomonas aeruginosa, and Acinetobacter baumannii, in addition to fungi such as Candida tropicalis and Candida glabrata, are associated with the deterioration of the tumor microenvironment, fostering chronic inflammation, immune evasion, and DNA damage [5, 6. 14, 28, 30, 32-35]. These microbial mechanisms facilitate tumor evolution and are linked to heightened resistance to standard treatments [7, 8, 33, 36].

Antimicrobial resistance presents a substantial challenge within the field of oncology, particularly for patients who possess compromised immune systems [34, 37-40]. The emergence of resistant microorganisms complicates the treatment of secondary infections, diminishes the efficacy of therapeutic interventions, and deteriorates the prognosis for individuals with melanoma [9, 38, 41]. The intersection of oncology and infectious diseases highlights the necessity for comprehensive treatment strategies that consider the influence of microbial infections on the progression of melanoma [10, 39, 42, 43]. Additionally, a critical element within the oncological context is the impact of malignant tumors on the process of wound healing. Pathogenic microorganisms commonly colonize wounds that are associated with tumors, which can impede the healing process, exacerbate inflammation, and heighten the risk of tumor metastasis [8, 11, 44-47]. Research indicates that pro-inflammatory cytokines, growth factors, and microRNAs are integral to the molecular pathways regulating wound healing and tumor progression; consequently, the tumor microenvironment emerges as a promising target for therapeutic intervention [9, 46, 49-52].

Antimicrobial peptides (AMPs) demonstrate considerable promise as a therapeutic alternative within this context [53-55]. These naturally occurring peptides possess immunomodulatory properties, rendering them effective in the control of infections and the suppression of tumors [54, 56, 57]. Their efficacy and low toxicity designate them as ideal candidates for innovative treatments of melanoma [12,13, 58-60]. Advancements in bioinformatics and rational peptide design have expedited the development of new therapies founded upon AMPs [59,61,62]. Through the utilization of computational tools and artificial intelligence, it is feasible to design molecules with high specificity and efficiency, thereby addressing the dual threats posed by melanoma and associated infections, as well as overcoming the limitations inherent in traditional therapies [14-16, 63-70].

This study investigates recent advancements in understanding the interactions between microbial infections and melanoma, the constraints of conventional cancer therapies, and the innovative potential of antimicrobial peptides within integrated patient care. By adopting an interdisciplinary approach, this research aspires to contribute to the formulation of more effective and safer therapeutic strategies, underscoring the application of computational tools in the rational design of multifunctional peptides.Ultimately, this work aims to translate bench-to-bedside findings, paving the way for personalized medicine approaches that leverage the synergistic interplay between immunomodulation and antimicrobial action to combat this aggressive malignancy.

Materials and Methods

Our review adhered to the PRISMA 2020 guidelines [17], employing a systematic and rigorous methodology to comprehensively examine the literature concerning the impact of microbial infections on melanoma progression. This examination emphasizes antimicrobial resistance and the potential advantages of antimicrobial peptides (AMPs) in the context of treatment. We conducted a thorough search across various academic databases, including PubMed, Scopus, Web of Science, Embase, and Google Scholar, to identify relevant studies on microbial infections and melanoma progression during the period from 2020 to 2025. Our search strategy integrated Boolean operators with keywords such as “melanoma progression,” “microbial infections,” “antimicrobial resistance,” “chronic inflammation,” “antimicrobial peptides,” and “therapeutic design.” We focused on studies that investigated the biological and molecular relationships between microbial infections and cancer, along with novel therapeutic approaches.

Clearly defined inclusion and exclusion criteria guided the selection of studies. Only peer-reviewed articles published in English were considered. Studies had to investigate microbial infections in melanoma patients or experimental models and address AMPs or related therapeutic interventions targeting melanoma and associated diseases. Studies unrelated to melanoma or antimicrobial peptides, articles lacking robust experimental or clinical data, and non-peer-reviewed materials, such as preprints and opinion pieces, were excluded from the review. Data extraction focused on key variables, such as microbial species and their mechanisms in melanoma progression, cytokines, immune pathways, and interactions within the tumour microenvironment. Information on therapeutic strategies involving AMPs, bioinformatics tools, and combinatorial approaches was also extracted. The findings were then organised thematically to address the primary research objectives and synthesised in a narrative format.

A critical analysis of the methodological framework for evaluating AMPs was conducted, focusing on the bioinformatics tools and artificial intelligence algorithms used in peptide design. Studies of silico methods for enhancing peptide specificity and stability were carefully reviewed. To ensure methodological rigour, transparency, and reproducibility, the review strictly adhered to the PRISMA 2020 statement. This statement includes a 27-item checklist covering a systematic review report's introduction, methods, results, and discussion sections. The PRISMA 2020 guidelines are accompanied by a flow diagram and the PRISMA 2020 Explanation and Elaboration paper. While primarily designed for systematic reviews evaluating health interventions, the guidelines apply to reviews of other interventions, such as social or educational interventions, and systematic reviews with objectives beyond intervention evaluation, such as assessing aetiology, prevalence, or prognosis. PRISMA 2020 supports reviews with or without synthesis, including those that perform pairwise meta-analyses or review only one eligible study.

Results

The study selection process strictly adhered to the PRISMA guidelines, ensuring transparency, reproducibility, and quality in the inclusion of articles. Initially, 2.186 records were identified through searches conducted in the PubMed (n=518), Scopus (n=251), Web of Science (n=332), Embase (n=601), and Google Scholar (n=484) databases. After removing 879 records, including 481 duplicates and 398 publications in languages other than English, 1,307 records remained for initial screening. During the screening stage, titles and abstracts were meticulously reviewed to identify studies meeting the inclusion criteria. At this phase, 736 records were excluded: 299 non-peer-reviewed materials and 437 articles that lacked robust experimental or clinical data. Consequently, 571 reports proceeded to the eligibility assessment stage.

During the eligibility phase, we excluded 385 records that didn't sufficiently address the relationship between microbial infections, antimicrobial resistance, melanoma, or antimicrobial peptides. These exclusions fell into two main categories: 183 studies that lacked a significant connection to antimicrobial peptides or microbial infections related to melanoma, and 202 studies focusing on conditions or diseases unrelated to melanoma progression. We then assessed the remaining articles against strict criteria outlined in the PRISMA guidelines, including clear objectives, robust methodology, and relevant data. Based on this evaluation, we selected 186 articles for inclusion in the final review. This rigorous selection process ensured a high standard of quality and relevance for the subsequent analysis.

A PRISMA checklist ensured a systematic and standardized approach to our analysis. The process involved developing a search strategy, defining inclusion and exclusion criteria, explaining the rationale for excluding studies, and conducting a thorough data analysis. Therefore, this approach yielded a robust and pertinent body of research underpinning our discussions. The complete process of identifying, screening, selecting, and incorporating studies is illustrated in the PRISMA flow chart (Figure 1). Subsequently, the selected studies were categorized into four main thematic domains: chronic

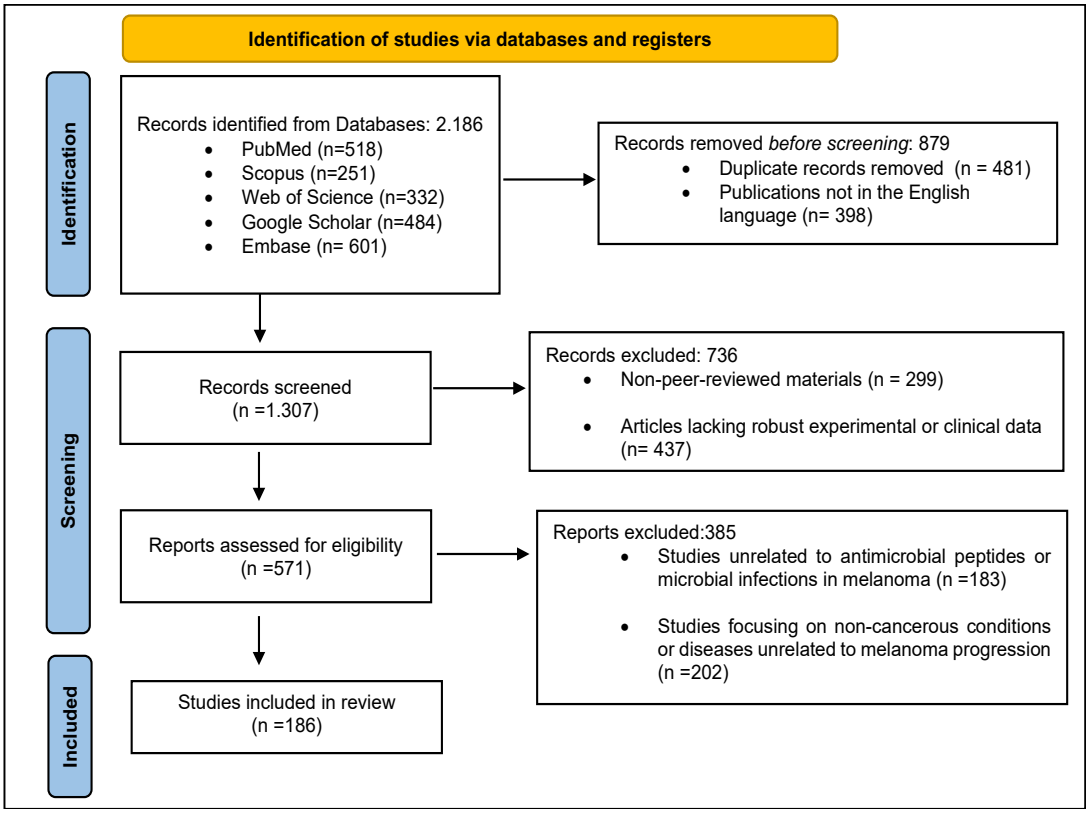

Figure 1. PRISMA Flowchart of Selected Studies

Table 1. Distribution of Included Studies Across Thematic Domains

Domain	Key Features Synthesized	Studies Reviewed
Chronic Inflammation	IL-6, TNF-α, and TGF-β activation of JAK/STAT3 & NF-κB pathways; EMT; stromal remodeling	52
Immune Evasion via M2 Polarization	M2 macrophage induction, IL-10, TGF-β, Treg activation, suppression of CTLs and neutrophils	59
Biofilm Formation & Antimicrobial Resistance	Biofilm persistence in wounds, oxidative stress, cytokine deregulation, drug resistance	64
AMP Therapeutics & Bioengineering	Dual antimicrobial and anti-tumour functions; EMT inhibition, angiogenesis suppression; AI-designed AMPs	50

Table 1 presents the number of studies associated with each of the four analytical domains identified in the systematic review. Due to thematic overlap among certain studies, these studies contributed to more than one domain, resulting in a total count that exceeds the 186 unique articles analyzed.

inflammation, immune evasion via M2 macrophage polarization, biofilm formation and antimicrobial resistance, and AMP-based therapeutic strategies. This classification was conducted in accordance with the protocol registered under PROSPERO (ID: 1072729). Notably, several studies addressed more than one domain, resulting in a cumulative total exceeding the 186 unique articles included in the review (Table 1).

These studies offer insights into chronic infections and melanoma progression but have limitations. Many rely on past data, introducing biases that affect result interpretation. Different methods hinder direct comparisons and limit the applicability of findings. Future studies should be prospective, multi-centered, and follow standard protocols to clarify cause and effect and improve understanding. Current research often uses experimental models, which help explain molecular mechanisms but may not reflect real-world settings. Small sample sizes, varied methods, and biases reduce data reliability and replicability. This is particularly relevant for antimicrobial peptides (AMPs), mostly in preclinical stages, limiting clinical trial potential. Furthermore, the absence of long-term studies and limited genetic diversity in animal models complicate the application of findings to diverse human populations.

Discussion

Building upon the synthesized findings from the 186 peer-reviewed studies included in this review, the discussion explores the influence of chronic infections on the tumour microenvironment (TME) and their contribution to the aggressiveness of melanoma [1–16,18–186]. The evidence has been systematically categorized into four interrelated domains: chronic inflammation, immune evasion through M2 macrophage polarization,

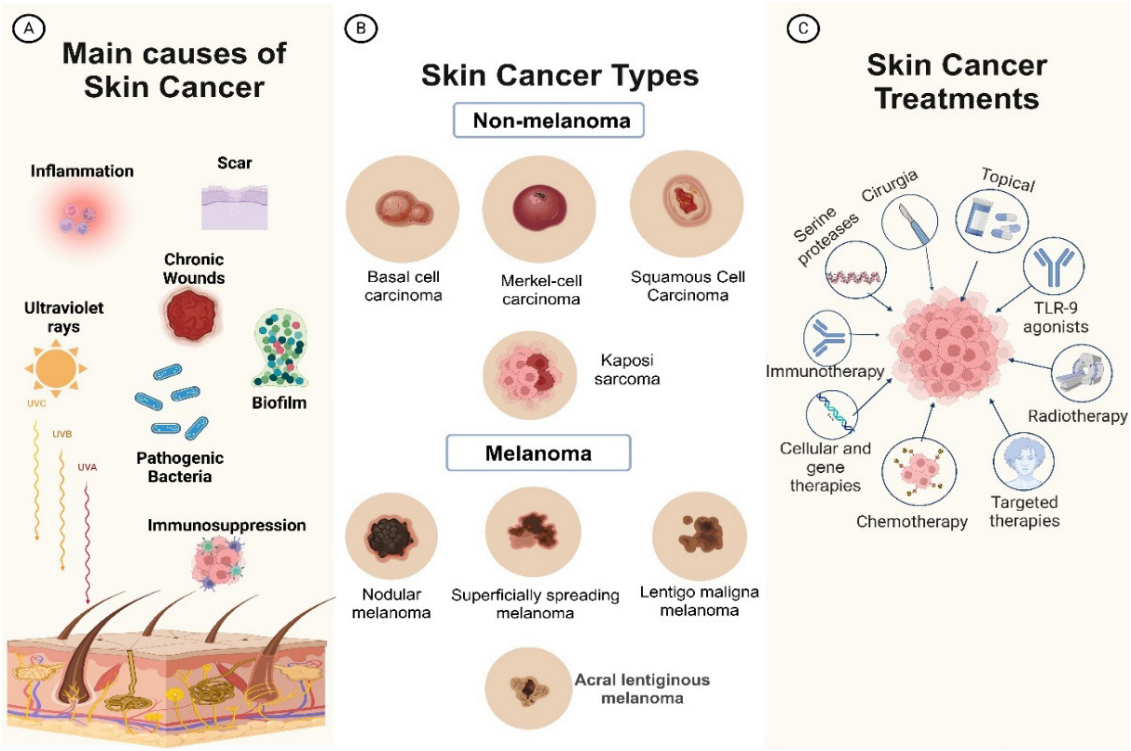

Figure 2. Main Causes, Types, and Treatments for Skin Cancer. (A) the primary causes of skin cancer, (B) the classification into non-melanoma and melanoma types, and (C) the available treatment options, which encompass surgery, immunotherapy, chemotherapy, and targeted therapies. Source: The author, created using Biorender.

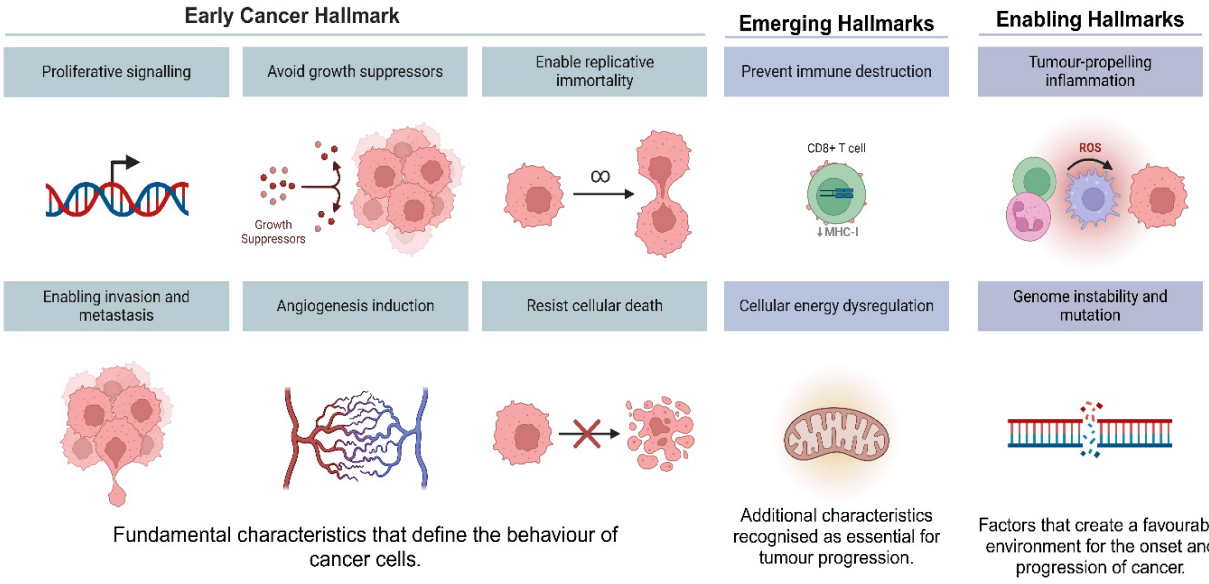

Figure 3. Characteristics and Factors of Cancer. Figure 3 illustrates the defining characteristics of cancer, which encompass unregulated proliferation, evasion of immune surveillance, resistance to apoptosis, and various factors, including genomic instability, inflammation, and angiogenesis, that are instrumental in tumor growth and the development of resistance to treatment. Source: The author, created using Biorender.

biofilm formation and antimicrobial resistance, and the dual-action therapeutic potential of antimicrobial peptides (AMPs). This section critically examines each domain's mechanistic insights, recurring patterns, and clinical relevance, thereby highlighting how infection-driven processes collectively facilitate tumour progression and resistance in melanoma.

Cancer continues to represent a significant global

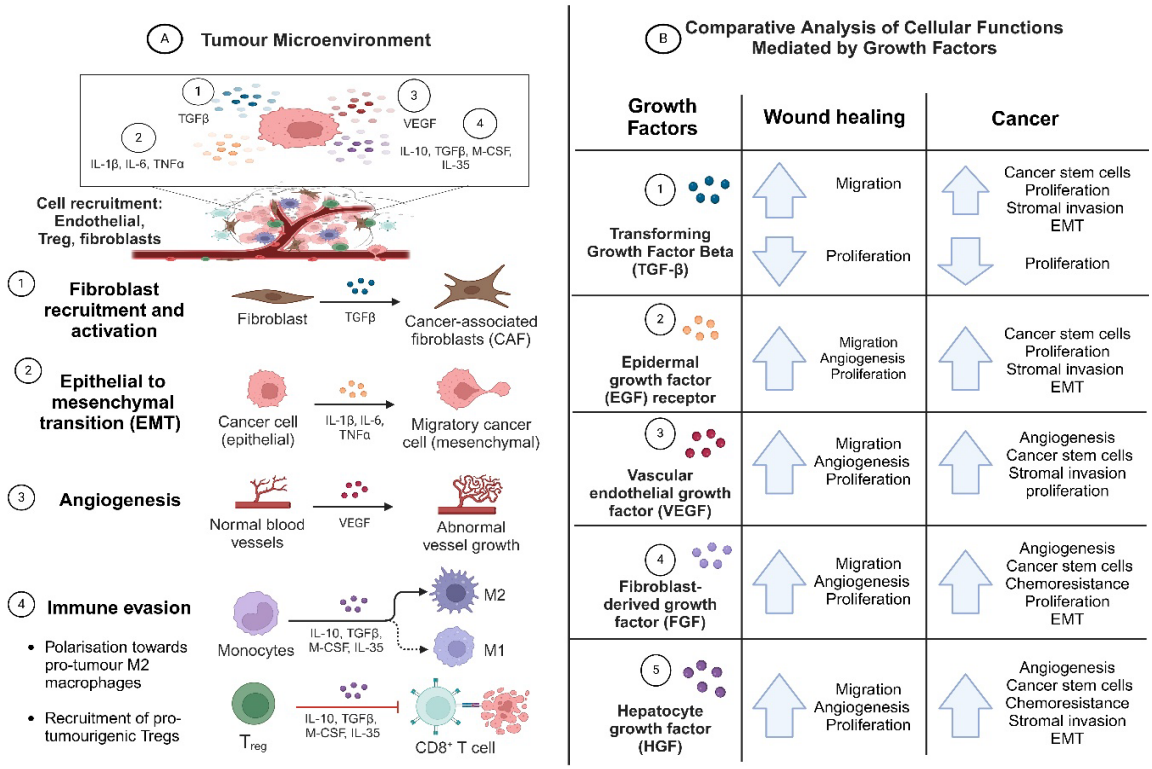

Figure 4. Impact of rowth Factors on the Tumour Microenvironment and Wound Healing.Figure 4 outlines (A) key events in the tumor microenvironment, including cell recruitment, epithelial-mesenchymal transition (EMT), angiogenesis, and immune evasion, all driven by growth factors like transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF). (B) compares the functions of various growth factors TGF-β, epidermal growth factor (EGF), VEGF, fibroblast growth factor (FGF), and hepatocyte growth factor (HGF) in wound healing and cancer.Source: Author, created using Biorender.

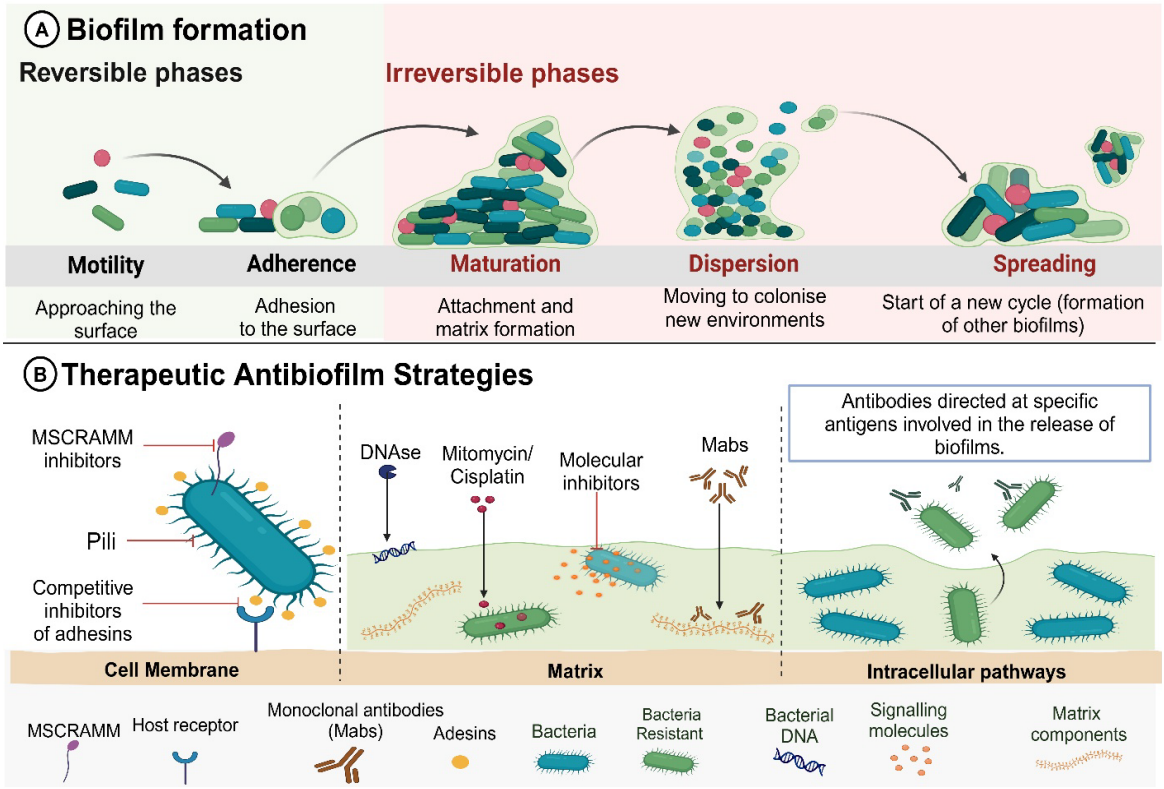

Figure 5. Biofilm Life Cycle and Anti-Biofilm Therapeutic Strategies. Figure 5 illustrates the biofilm life cycle, which encompasses adhesion, maturation, and dispersion, as well as strategies for combating biofilms. Source: The author, created with Biorender.

health challenge, resulting in approximately 10 million fatalities in 2020 [2, 5, 8, 13, 22-24]. This disorder is multifactorial, characterized by uncontrolled cellular proliferation, localized tissue invasion, and the potential for metastasis [5, 25-28]. The pathogenesis is influenced by a complex interplay of various factors [27, 29-31]. These factors encompass genetic mutations, environmental exposures, and behavioral components [26, 36-38]. Notable behavioral components include tobacco usage, insufficient dietary habits, physical inactivity, and exposure to ultraviolet (UV) radiation [36, 39-42] (Figure 2). Brazil exemplifies this concern, particularly in regions of high exposure, where melanoma stands out as an especially lethal skin cancer [43-47]. It accounts for over 50% of skin cancer-related fatalities, despite its lower prevalence relative to basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) [27, 35, 37, 48-56]. The aggressive and metastatic characteristics are pronounced in specific subtypes of melanoma, particularly the nodular variants [25, 38, 57-62]. Early detection and prompt intervention are crucial, as emphasized by the following studies [63-66].

At the molecular level, melanoma arises from modifications in critical regulatory pathways that govern DNA repair, cell cycle control, apoptosis, and differentiation [67-72]. These alterations pertain to essential mechanisms such as mismatch repair and nucleotide excision repair involved in DNA repair [46, 52, 73-77]. They also encompass cyclin-dependent kinase activity and retinoblastoma protein function, crucial for cell cycle progression [53, 57, 64, 78-81]. Furthermore, Bcl-2 family proteins and caspase activity play significant roles in apoptosis, while MITF and melanogenesis are fundamental for melanocyte differentiation [61, 67, 79, 82]. Such modifications may result from genetic mutations, including *BRAF, NRAS, CDKN2A*, epigenetic changes, or environmental factors [68-72, 83]. Ultimately, these factors culminate in unregulated cellular growth, enhanced survival, and tumor formation [73, 79, 84-86].

Mutations in tumor suppressor genes, such as TP53, combined with disruptions in mitotic regulation, significantly contribute to genomic instability, therapeutic resistance, and phenotypic heterogeneity [52, 59, 75, 82-87]. This fundamental instability drives tumor evolution, resulting in aggressive subclones' emergence and ultimately limiting targeted therapies' efficacy [88-93]. Therefore, understanding the intricate interplay between these genetic and regulatory defects is essential for developing more effective cancer treatments [90,92,94-98]. Additionally, the tumor microenvironment (TME) exacerbates these issues by facilitating angiogenesis through vascular endothelial growth factor (VEGF), while concurrently suppressing immune responses [60, 96, 99-104]. Furthermore, it promotes epithelial–mesenchymal transition (EMT), influenced by stromal components and pro-inflammatory cytokines [105-109].

These mechanisms and emerging hallmarks, such as tumor-promoting inflammation and metabolic reprogramming, furnish critical insights into the progression of melanoma and its therapeutic resistance (Figure 3) [62, 72, 77, 110-115]. The Warburg effect represents a metabolic hallmark characterized by an

increased glucose uptake and lactate production, even in the presence of oxygen [100, 112, 114, 116-120]. This phenomenon enables melanoma cells to proliferate more rapidly and evade immune surveillance, thereby contributing to their progression and resistance to targeted therapies [95, 121-125]. Furthermore, deficiencies in apoptotic signaling and necrotic cell death promote chronic inflammation, facilitating immune evasion and metastasis [126-129].

Significant advancements have been achieved in immunotherapies, particularly through the development of checkpoint inhibitors [124, 127, 130-135]. These inhibitors activate the body's intrinsic immune system to combat cancer [136-138]. Another notable development is represented by CAR T-cell therapies, which involve the genetic engineering of immune cells specifically to target cancer cells [123, 139, 140]. Furthermore, oncolytic viruses have been engineered to selectively infect and destroy cancer cells while concurrently stimulating anti-tumor immune responses [132, 138, 140-144]. Such therapies offer new hope for individuals suffering from previously untreatable cancers [122, 138, 142, 145]. Nevertheless, challenges remain regarding side effects, efficacy across certain cancer types, and financial implications [144,146]. These advancements include checkpoint inhibitors, such as nivolumab and pembrolizumab, and targeted therapies, like vemurafenib for *BRAF* mutations [140, 144,146-148]. For instance, immunotherapy and targeted therapy have significantly improved survival rates in patients with advanced melanoma [147, 150-152].

Nonetheless, the challenges associated with treatment resistance and adverse effects remain significant [145, 150, 153-156]. Antimicrobial Peptides (AMPs) emerge as innovative therapeutic options that offer dual advantages: they exhibit antimicrobial properties and possess the ability to modulate the immune system within the tumor microenvironment (TME) [102,104,149,157-161]. For instance, research has demonstrated that AMPs inhibit critical processes in melanoma progression, including epithelial-mesenchymal transition (EMT), angiogenesis, and immune suppression [96, 103, 110, 162, 163]. Due to their combined antimicrobial and immune-modulating capabilities within the TME, AMPs are increasingly regarded as promising new therapies for melanoma treatment [164-170]. This dual benefit positions AMPs as attractive candidates for overcoming treatment resistance and mitigating the adverse effects associated with existing melanoma therapies [171-176].

Advances in bioinformatics and artificial intelligence (AI) have significantly contributed to the development of AMPs that exhibit enhanced stability and specificity for the treatment of cancer [177-180]. By integrating innovative technologies such as photodynamic therapy, liposomal drug delivery, AI-assisted diagnostics, and teledermatology, we have significantly improved access to diagnostic and treatment services, particularly in regions that require them the most [166, 181-186]. The COVID-19 pandemic has exacerbated global disparities in cancer care, resulting in delays in melanoma diagnoses and underscoring the urgent need for more inclusive public health policies [33, 40, 55, 74, 102, 107]. To reduce mortality rates and enhance patient outcomes, we are developing early detection strategies, including the ABCDE rule, alongside comprehensive educational campaigns [40, 51, 62, 76, 81, 99, 108].

Chronic Inflammation and Pro-Tumour Signaling

Researchers have investigated the impact of chronic infections on the development of a long-term inflammatory environment that promotes melanoma growth, as evidenced by 52 studies. These investigations underscore chronic inflammation as a pivotal factor in tumor development. Furthermore, 24 studies concentrated on the role of microbial persistence, particularly from *S. aureus*, *C. tropicalis*, and *P. aeruginosa*, in impairing wound healing and exacerbating tumor aggressiveness [5, 6, 59, 95, 104, 106, 116, 120, 121].

These infections disrupt the body's immune equilibrium and initiate signaling pathways that facilitate tumor growth, angiogenesis, and the immune system's failure to detect and eliminate the tumor [60, 106-109,120]. Antimicrobial peptides (AMPs), which are released by skin cells through the activation of Toll-like receptors TLR2 and TLR3, serve a crucial defensive function by activating TNF-α signaling and modulating immune cell activity [118, 122, 136]. However, when microbial colonization endures, this protective mechanism deteriorates, permitting tumor cells to thrive in an environment that fosters inflammation and undermines the immune system [25,105,137]. Chronic infections disturb the immune system's fragile balance, promoting tumor growth through various mechanisms [110,121,124]. Inflammatory signaling pathways activated by the infection stimulate tumor proliferation, angiogenesis, and immune evasion [125-129]. Initially, AMPs released by skin cells assist in combating the microbes and managing immune responses [126,128]. Nonetheless, an extended infection overwhelms this defense, resulting in a sustained inflammatory state that suppresses immune function and ultimately fosters tumor development [95, 127, 134, 135]. Consequently, the ensuing environment becomes favorable for tumor growth and survival [105, 108, 110, 113, 134].

Long-term infections enhance the levels of specific proteins, including *IL-6, TNF-α*, and **TGF-β,** which activate crucial pathways that facilitate tumor growth, such as *JAK/STAT3* and NF-κB [95, 104, 106, 119, 121]. When IL-6 engages STAT3, it aids in the survival of tumor cells, while TNF-α and NF-κB signaling promote the epithelial-mesenchymal transition (EMT) and sustain chronic inflammation [10, 25, 107, 125, 128]. Although TGF-β is instrumental in wound healing, it contributes to chemotherapy resistance, the invasion of adjacent tissues, and the suppression of the immune system within tumors [105, 120, 125, 130, 136]. Growth factors essential for regular tissue repair, such as EGF, FGF, HGF, and VEGF, are utilized by tumor cells to support angiogenesis, maintain cancer stem cell niches, and evade apoptosis [42,45–106,130,137-139].

Chronic wounds frequently exhibit microbial activity and overproduction of proteases, which degrade growth

factors and impede healing. This phenomenon may also facilitate tumor adaptation [42,81,95,113,115,129,135]. Infections caused by *S. aureus, C. tropicalis, P. aeruginosa, A. baumannii*, and *C. glabrata* commonly result in the formation of biofilms within melanoma lesions [59,106,114,126,128,132]. These polymicrobial biofilms provide secure environments for pathogens, enhance antibiotic resistance, and exacerbate inflammation by continuously releasing molecular patterns associated with pathogens [95, 116,120,123,138]. Furthermore, microbial byproducts such as N-nitrosamines have the potential to induce DNA damage, thereby contributing directly to mutations and the development of cancer [139,140]. Prolonged infections also compromise the functionality of neutrophils and macrophages, critical immune cells for tissue repair, resulting in diminished phagocytic activity and increased tumor tolerance [114,116,126,137,140].

As chronic inflammation persists, the tumor microenvironment in melanoma gradually evolves into a more immunosuppressive state [95,113,115,131]. Prolonged exposure to antigens culminates in the exhaustion of CD8+ T cells, while microbial enzymes hinder antigen presentation and attenuate innate immune responses [128.133]. Continuous microbial activation also desensitizes protective Toll-like receptor signaling, undermining immune surveillance [35,52,59,91,117,125,127-132]. These mechanisms synergistically interact with tumor-derived signals to diminish anti-tumor immunity and facilitate metastasis [10,67,120,122,126,130,134]. In clinical practice, melanoma lesions, particularly those characterized by ulceration or vegetation, frequently acquire secondary infections, especially in patients possessing compromised immune systems undergoing chemotherapy or receiving broad-spectrum antibiotics [35,72,99,104,112,132-135].

Considering the complex relationship between factors, therapies that tackle both the inflammatory and microbial aspects of melanoma are gaining importance [23,45,59,106,112,120,136]. For instance, regulating IL-6 and TNF-α signaling may help reduce angiogenesis and EMT [121,123,129,137]. Meanwhile, antimicrobial strategies focused on biofilms could improve immune response and boost drug effectiveness [125,128,138]. Additionally, treatments aimed at preserving macrophage and neutrophil function, or increasing AMP production, may help restore immune control over infections and tumor growth [117,123,130,134,139]. Future studies should focus on comprehensive approaches that view infection-driven inflammation as a secondary and primary target for treating melanoma.

Immune Evasion via M2 Macrophage Polarization

Suppressing the immune system is a well-known result of long-term infections within the melanoma tumor microenvironment (TME) [53,106,108,109,115,137-142]. Over 40 studies have shown that microbial pathogens, especially C. glabrata, C. tropicalis, and S. aureus, lead to tumor-associated macrophages (TAMs) being polarized towards the M2 Macrophage [116,126,143-150]. This M2 phenotype is marked by the release of IL-10, TGF-β, and other immunosuppressive chemicals [116,127,132,141,148,151-156]. These M2 macrophages, working together with regulatory T cells (Tregs), play a key role in weakening the immune system's ability to fight cancer, allowing the tumor to progress more easily (Figure 4) [110,113,129-131,1501,157]. This is especially important in people with weakened immune systems, such as those living with HIV/AIDS or undergoing cancer treatment, where infections can worsen the immune dysfunction and lead to more aggressive forms of melanoma [18,104,116,132-136,158].

Chronic infections compromise the immune system's integrity and impair its inherent recognition mechanisms [109,124,130,137,159]. Research indicates that such infections influence Toll-like receptor (TLR) signaling, diminishing the body's capacity to combat tumors and facilitating the evasion of cancer cells from immune detection [102,131,145,162-167]. This perturbation of immune pathways allows for unregulated proliferation of melanoma cells, frequently in conjunction with genetic mutations [110,131165,166,168-170]. These mutations may encompass alterations in the PTEN gene, present in 10–20% of primary melanomas, which disrupt cellular cycle regulation and foster cancer advancement [101,102,132,145,168-171]. Furthermore, persistent bacterial or viral infections, such as those instigated by Helicobacter pylori or Epstein-Barr virus, are associated with the sustained release of pro-inflammatory cytokines, specifically IL-6 and TNF-α, which further expedite cancer proliferation, angiogenesis, and immune suppression [53,104,126,135,145,165,168,172-174].

Specific fungal pathogens, such as C. tropicalis and C. glabrata, considerably impact the immune responses of cancer patients [128-134,154,175]. Notably, C. glabrata is recognized for its heightened resistance to antifungal treatments, capacity to form biofilms, and production of enzymes that modulate the immune system [112,126,135,136,169,176]. Proteases and hemolysins are crucial in altering macrophages and activating regulatory T cells [109,110,114,119,170-174,177]. Similarly, C. tropicalis has been linked to systemic and skin infections in individuals with compromised immune systems, exacerbating inflammation and increasing the risk of cancer through mechanisms that facilitate uncontrolled cell proliferation and instability [111,115,116,126-129,175,178]. Furthermore, these species synthesize substances that foster the growth of blood vessels and the transformation of epithelial cells into mesenchymal cells critical processes in the dissemination of melanoma and the development of resistance to treatments [71,87,95,99 ,106,118,131,176,179].

Aside from fungal infections, bacterial pathogens such as S. aureus and S. epidermidis also play a considerable role in disease progression [59,82,95,106,114,121,132 ,141,165]. Staphylococcus aureus produces toxins and virulence factors that lead to excessive inflammation and initiate the release of cytokines, including interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) [74,79,81,85,93,95,100,103,11 2,119]. These cytokines facilitate tumor cell invasion and stromal degradation [80,97,108,112,115,119,132, 166]. Although S. epidermidis is deemed less virulent,

it frequently forms biofilms in immunosuppressed patients, contributing to persistent inflammation and resistance to treatment [80,81,97,109,145,154]. Such interactions considerably impede the clinical management of melanoma, underscoring the necessity for therapies that target both infection and tumor progression [85,88,120,138,161].

Infections may collaborate with pre-existing cancer-promoting pathways [22,39,52,64,71,85,107,116,119,132,157,159,165,167-170]. Prolonged immune suppression, DNA damage, and persistent inflammation have the potential to interact with environmental carcinogenic factors such as ultraviolet (UV) radiation, tobacco use, and obesity, thereby facilitating the development of cancer [87,93,105,125,129]. Cancer progression occurs through three phases: initiation, promotion, and progression, which may be affected by microbial activity [78,81,99,102,116,118,121,156,162]. In low- and middle-income nations, up to 25% of cancers are associated with chronic infections, emphasizing their global significance as biological triggers for cancer [67,69,93,121,125,132,150,165]. This insight underscores the need for integrated strategies combining antimicrobial control with immunomodulation to impede melanoma progression and enhance patient outcomes [74,81,94,96,107,120,144,161].

Invisible Barriers: Biofilms in Melanoma-Linked Chronic Infections

According to the World Health Organization's (WHO) 2024 global priority list, addressing these pathogens requires advancing research on novel antimicrobials [18,20,21,37,63]. Additionally, this endeavor involves establishing comprehensive infection control programs and promoting the responsible use of existing medications [68,72,89,95,100,130]. Among fungal pathogens, the increasing resistance observed in Candida species—primarily C. albicans and C. tropicalis—demands rigorous monitoring and the development of new antifungal agents [24, 102,137,158,161,165-169].

The ESKAPE group, consisting of Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species, represents a significant threat to global public health due to their remarkable capacity to develop and disseminate resistance mechanisms [20,25,81,96,108,138,143,156]. Numerous pathogens in this group resist last-resort antibiotics such as carbapenems and polymyxins [39,44,109,126,132,143,150,157]. Furthermore, these pathogens frequently exchange resistance elements through horizontal transfer, resulting in ongoing infections and outbreaks in healthcare settings [82,132,151,154,158-161].

Antimicrobial resistance (AMR) among melanoma patients, particularly those with compromised immune systems, presents significant implications [98,102,138,143,145]. The concurrent infection of chronic wounds by resistant bacteria, such as methicillin-resistant S. aureus (MRSA), C. glabrata, and other ESKAPE pathogens, exacerbates patient outcomes and complicates cancer treatment [21,78,132,158-162]. For instance, C. glabrata possesses intrinsic resistance to azole antifungals, including fluconazole, which constrains treatment options and heightens the risk of therapeutic failure [93,122,152,170]. Moreover, infections may instigate intensified inflammatory responses, diminish patients' capacity to endure chemotherapy and immunotherapy, and potentially contribute to prolonged hospitalizations [74,80,169-172].

The formation of biofilms represents a critical factor in the persistence and resistance of microbial infections, particularly in chronic wounds and cancerous lesions, as evidenced in patients diagnosed with melanoma (Figure 5) [25,36,40,173-175]. A comprehensive review of 35 studies has determined that biofilms produced by Pseudomonas aeruginosa, Acinetobacter baumannii, and various species of Candida are prevalent in melanoma-related wounds [122,136,159,173-177]. These biofilms function as physical and biochemical barriers that impede the ingress of therapeutic agents and provide a protective shield for microbes against the host's immune response [8,147,155,165,174,176,178]. Consequently, this phenomenon substantially contributes to treatment failures, extended periods of local inflammation, and necrosis of tissues [24,63,74,89,95,98,106,122,150,168,171].

Biofilms comprise densely aggregated microbial cells enveloped by a self-generated extracellular polymeric substance (EPS) matrix [167,169,170]. This matrix comprises polysaccharides, extracellular DNA (eDNA), proteins, and lipids [163,164,168]. It provides structural stability to the biofilm while obstructing the penetration of antimicrobial agents, thereby reducing their efficacy [91,103,159,163,167,170]. The development of biofilms transpires through several stages: (1) the reversible attachment of planktonic cells, (2) the acquisition of irreversible attachment mediated by adhesins and pili, (3) maturation through the accumulation of EPS and the formation of a complex structure, and (4) disintegration, which allows sessile cells to revert to a planktonic state, consequently enabling them to colonize new environments [89, 90,98,115,123,134,164,158-175].

Polymicrobial biofilms, particularly those formed by P. aeruginosa, A. baumannii, C. albicans, and C. tropicalis, possess significant clinical relevance due to their collective virulence and resilience [94,115,135,159,172,176]. The intricate structure of these biofilms enhances resistance through various mechanisms, including the overproduction of extracellular polymeric substances (EPS), quorum sensing (QS), and cyclic-di-GMP signaling pathways [76, 85–87, 91–93,165,173]. These characteristics are especially pronounced in Pseudomonas aeruginosa, where internal signaling molecules meticulously regulate biofilm development [102,142,149,165,174]. This process facilitates the transition from planktonic to sessile growth forms, amplifies EPS production, and governs virulence gene expression [89, 95, 98,143,165,177].

Quorum sensing (QS) systems are essential for regulating the formation and resistance of biofilms [95,103,153,160]. These systems function by synthesizing and detecting signaling molecules, which include acyl-homoserine lactones (AHLs) in Gram-negative

bacteria and auto-inducing peptides in Gram-positive species [86,96,132,150,176]. Both types of signaling molecules play a critical role in coordinating collective behavior that is contingent upon population density [86,95,96,102,132,148,151]. In the case of Pseudomonas aeruginosa, the Las and Rhl QS circuits govern the expression of genes that are involved in the production of extracellular polymeric substances (EPS), virulence, and biofilm architecture [89, 97,144,163,170]. Concurrently, cyclic-di-GMP functions as a second messenger that facilitates the transition between motile and sessile lifestyles [93,98,144,164,170,175]. Elevated levels of cyclic-di-GMP activate diguanylate cyclases (DGCs), thereby promoting biofilm formation. Conversely, phosphodiesterases (PDEs) diminish their concentration, resulting in dispersion [90, 97-99,144,170-177].

A significant characteristic of biofilm resistance is its metabolic diversity [126,152,177]. Bacteria located within the inner layers of a biofilm frequently exhibit diminished metabolic activity as a result of restricted nutrient and oxygen availability, rendering them less susceptible to antibiotics that target rapidly proliferating cells [92–94,149,155,165,169-177]. Furthermore, the biofilm environment facilitates horizontal gene transfer (HGT), which accelerates the dissemination of antibiotic resistance genes and contributes to the emergence of multidrug-resistant (MDR) strains [93, 94,155,171,176,178]. Biofilms are pivotal in chronic infections and pose challenges to treatment methodologies [82,97,99,120,171,179]. It is noteworthy that P. aeruginosa is recognized for forming persistent lung biofilms in individuals with cystic fibrosis, whereas A. baumannii is associated with biofilms on medical equipment and hospital surfaces, exacerbating hospital-acquired infections [76,97,99.143,172,175,178]. Fungal biofilms, particularly those formed by C. albicans and C. tropicalis, are linked to device-related infections and demonstrate inherent resistance to conventional antifungal therapies, such as azole compounds [99,171,173].

Researchers are currently engaged in the development of innovative therapies aimed at addressing these challenges [96,150,158,176]. Among these approaches are the utilization of enzymes that decompose exopolymeric substances (EPS), antimicrobial peptides, nanoparticles designed for drug delivery, and monoclonal antibodies that specifically target elements of biofilms or signaling molecules [20,27,42,66,89,95,100,143,172,178]. The integration of these targeted therapies with traditional antibiotics exhibits considerable potential for combating resistance induced by biofilms [97-101,124,143]. The correlation between biofilm formation and antimicrobial resistance presents a significant obstacle [5,9,13,25,37,58 ,101,124,139,165]. This issue is particularly pertinent for the management of infections in patients suffering from melanoma and other immunocompromised conditions [52,58,102,124,152,165,167]. A comprehensive strategy is essential for mitigating biofilm-associated infections [162,165,169-174]. Such a strategy encompasses early diagnosis, innovative treatment modalities, and stringent infection control measures, all of which address the pressing global issue of antimicrobial resistance [24,100,175].

Dual-Action Antimicrobial Peptides: Design, Immunomodulation, and Applications in Melanoma

Antimicrobial peptides (AMPs) have emerged as promising therapeutic agents possessing both antimicrobial and antitumor properties, particularly in the management of melanoma and its associated complications [47,84,94,118,134,176]. These peptides are generally comprised of short sequences of amino acids characterized by amphipathic structures, which facilitate rapid interaction with bacterial membranes leading to destabilization and cellular lysis [7,118,134,177]. In terms of structure, AMPs are categorized into cationic, neutral, or cyclic peptides [47,84,118,176,178]. Cyclic variants exhibit significantly greater resistance to enzymatic degradation, attributable to the stabilization conferred by disulfide bonds [98,118,134,169,178].

AMPs demonstrate broad efficacy against multidrug-resistant pathogens, including S. aureus, P. aeruginosa, and Candida species [119,129,171,179]. This characteristic renders them particularly advantageous for the treatment of secondary infections associated with melanoma-related wounds [13,47,76,81,119,180]. The thirty-eight studies reviewed emphasized AMPs such as LL-37, melittin, and lactoferricin B (LfcinB) due to their dual-action properties [25,107,132,177,181]. These molecules exhibit selective cytotoxicity towards melanoma cells, disrupt microbial membranes, and modulate immune responses [5,7,171,182]. Furthermore, they inhibit critical processes that facilitate cancer progression, including epithelial–mesenchymal transition (EMT), angiogenesis, and the release of pro-inflammatory cytokines [151,159,172]. Examples of these cytokines encompass interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which are frequently elevated within melanoma microenvironments [89,143,151,159,170,183].

Therapies based on peptides have garnered considerable attention in the treatment of cancer, as anticancer peptides (ACPs) have demonstrated the capacity to trigger apoptosis, inhibit tumor proliferation, and modify the immune microenvironment surrounding tumors [151,172,184]. In particular, melittin analogs and LfcinB have exhibited the ability to selectively target and eliminate melanoma cells while preserving healthy tissue [14,136,176,179]. These peptides possess dual functionalities, being effective in tumor cytotoxicity as well as combating infections [177-181]. Consequently, they are regarded as promising candidates for integrated therapeutic approaches in the management of melanoma [141,165,180,183]. Melanoma frequently presents in conjunction with chronic wounds or infections in individuals with compromised immune systems [76,118,141,156,180,185].

Recent advancements in bioinformatics and artificial intelligence (AI) have substantially accelerated the rational design of antimicrobial peptides (AMPs) [179,183-186]. This development enhances the prediction of peptide–target interactions, resistance to proteolytic degradation, and minimizes cytotoxicity to host cells [182,184]. A total of twelve studies have concentrated on the development of AI-assisted AMPs, employing methodologies such as

structure–activity modeling and molecular docking to improve therapeutic selectivity and refine physicochemical properties [181,183,185,186]. Furthermore, de novo-designed and bioinspired synthetic peptides are being meticulously customized for heightened specificity and stability, addressing critical challenges concerning production costs and degradation [163,178,180,182].

The integration of AMPs with conventional or targeted therapies for melanoma has demonstrated considerable potential for synergistic effects [161,173,179]. Initial investigations indicate that the combination of AMPs with immune checkpoint inhibitors has resulted in enhanced antitumor efficacy and improved management of infections [126,129,182]. Notable immune checkpoint inhibitors encompass pembrolizumab and nivolumab [132,181]. Furthermore, targeted therapies such as the *BRAF* inhibitor vemurafenib and the MEK inhibitor cobimetinib significantly contribute to these therapeutic outcomes [109,127,145,154]. This multifaceted approach addresses both the progression of cancer and infection-related complications, a factor of particular importance for patients with compromised immune systems receiving treatment for melanoma [51,59,62,77,171,184].

Demonstrating substantial potential exceeding direct cytotoxic effects, AMPs are recognized primarily for their involvement in immunomodulation. This encompasses the capability to reverse tumor-induced immunosuppression and enhance antigen presentation [134,148]. Research indicates that AMPs can modulate cytokine profiles and facilitate T-cell-mediated immune responses, thereby promoting a more effective anti-tumor immune environment [10,136,143,152,169]. Furthermore, advancements in nanotechnology have expanded the therapeutic applications of AMPs [179,182,184]. Through the encapsulation of peptides within nanoparticles, researchers can augment stability and bioavailability while simultaneously enabling targeted delivery [170,183,186]. Significant innovations include nanoformulations developed for AMP-based vaccines and drug delivery systems specifically aimed at melanoma treatment [158,171,183]. These delivery mechanisms reduce systemic toxicity and enhance the concentration of pharmaceuticals at tumor or infection sites [134,181-186].

In the management of wounds for patients suffering from melanoma, AMPs assume a foundational role, given that infections and ulcerations frequently arise due to tumor necrosis and complications associated with the immune system [115,132,148,165]. Silver sulfadiazine is acknowledged for its antimicrobial and antitumor properties and has been utilized for the topical treatment of wounds [116]. However, the risk of hypersensitivity necessitates a cautious approach [116,157]. Alternative agents, such as metronidazole, have significantly reduced the prevalence of anaerobic bacteria and the resultant odor, thereby improving wound hygiene and the quality of life for those affected [137,152,156,162]. Moreover, methodologies such as papain-based enzymatic debridement, ointments containing vitamins A and D, and activated charcoal provide supplementary benefits in promoting wound healing and infection control [86,104,171,174].

When fungal infections manifest in individuals diagnosed with melanoma, particularly those attributable to C. tropicalis and C. glabrata, management becomes particularly challenging due to resistance to azole antifungal agents such as fluconazole [122,138,144]. For the effective treatment of these infections, medical practitioners frequently employ echinocandins (including caspofungin) and combination therapies [53,76,114,164,172]. To avert the occurrence of these infections, it is imperative to uphold rigorous hygiene practices, facilitate prompt diagnosis, and manage risk factors such as diabetes and the excessive utilization of antibiotics [42,57,74,104,149,170,175].

Therapies for metastatic melanoma, including checkpoint blockade, chemotherapy, and targeted kinase inhibitors, could benefit from combinations with AMPs to enhance outcomes and reduce resistance [10,11,58,74,85,109,132,144,169,181]. For example, conjugating AMPs with monoclonal antibodies like nivolumab and ipilimumab may boost the immune response, allowing for lower dosages of cytotoxic agents and minimizing side effects [27,28,48,176,181]. AMPs show promise as therapeutics providing multiple advantages in melanoma treatment [133,141]. Their antimicrobial properties, immunomodulatory effects, and cytotoxic capabilities make them strong adjuncts to existing therapies [144,156,168,172]. These traits work synergistically with advanced peptide design and delivery systems to tackle tumor growth and infection [142,154,171,180,186]. Future research should focus on integrating these treatments into clinical practice, using artificial intelligence to identify more effective peptides, and conducting combination trials to validate their dual-action efficacy in real-world oncology [10,123,129,143,179,185,186].

Critical View Section

This review provides an analysis of microbial infections and melanoma progression; however, several limitations are present. A primary concern pertains to the influence of language restrictions on the results; the exclusive focus on English publications may have resulted in the omission of relevant research published in other languages, thereby affecting the comprehensiveness of the findings. The majority of the studies included in this review are preclinical or experimental in nature, which limits their applicability to clinical practice with human patients. While preclinical research is essential for comprehending underlying pathways, the absence of large-scale clinical trials suggests that the therapeutic potential of antimicrobial peptides (AMPs) for melanoma remains unverified in human subjects.

Another major limitation is clear in the scope of the therapeutic strategies being discussed. Although antimicrobial peptides (AMPs) show promise as dual agents for controlling infections and suppressing tumors, there's a lack of data on their long-term effectiveness, safety, and potential for clinical use. Many studies focus mainly on single-agent therapies, while the potential for AMPs to work together with other treatments, such as immunotherapies and chemotherapy, hasn't been fully explored. Furthermore, the review doesn't adequately

address the broader challenges of translating AMPs into clinical use, including issues like peptide stability, targeted delivery methods, and patient-specific differences, all of which are key to determining whether a treatment will work.

Future research needs to focus on large-scale clinical trials to validate the effectiveness and safety of antimicrobial peptides (AMPs) for melanoma patients. These studies should include diverse populations and various stages of melanoma to confirm the findings can be applied broadly. Exploring combination therapies that combine AMPs with existing immunotherapies could reveal synergistic effects that boost tumor suppression. Advances in computational peptide design should also be used to improve the stability, specificity, and targeted delivery of AMPs to tumor sites. Long-term studies on the lasting impact of AMP-based treatments will help overcome the current barriers to clinical use.

This review synthesizes findings from microbiology, immunology, and oncology to offer a comprehensive perspective on the interrelationship between infection, inflammation, and the progression of melanoma. However, further research is essential to bridge the existing knowledge gaps and to translate experimental findings into clinically viable therapies.

Overall Insights

The intersection of microbial infections and melanoma progression emphasizes the urgent need for integrated, multidisciplinary therapeutic strategies. Chronic inflammation, immune evasion, and biofilm formation are highlighted in this study as key factors driving tumor malignancy, confirming the complex interplay between infection and melanoma. Antimicrobial peptides (AMPs) emerge as promising bifunctional agents, offering the potential for infection control and directly suppressing tumor growth. Targeted and more effective therapies can be developed by harnessing advancements in computational design and bioinformatics, ultimately improving clinical outcomes for melanoma patients. To fully realize the potential of AMPs, future research should focus on optimizing peptide stability, refining delivery mechanisms, and ensuring seamless clinical integration. Exploring the synergistic effects of AMPs with other therapeutic modalities and investigating their long-term safety and efficacy will be crucial to overcoming current therapeutic limitations. These efforts will pave the way for more effective treatments, thereby enhancing the prospects for melanoma patients in the near future. This review offers novel insights into the interplay between microbial infections and melanoma progression, particularly highlighting the therapeutic potential of antimicrobial peptides (AMPs) as dual agents for infection control and tumor suppression.

Author Contribution Statement

Layza Sá Rocha conceived the study and drafted the manuscript. Ana Cristina Jacobowski contributed to data analysis and manuscript editing. Eduarda Thiburcio do Nascimento Reis performed article searches and data selection. Octávio Luiz Franco provided bioinformatics support and critically revised the manuscript. Marlon Henrique Cardoso contributed to immunological analysis and writing support. Maria Ligia Rodrigues Macedo supervised the project and approved the final version of the manuscript.

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Ethical Approval

Not applicable, as this study is a systematic review and does not involve direct human or animal experimentation.

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Scientific Approval

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Data Availability

All data analyzed during this review are included in the published articles cited in the references.

Registration: This review was prospectively registered in PROSPERO (ID: 1072729).

Conflict of Interest

The authors declare no conflict of interest.

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