Candida albicans and Candida Tropicalis Antigen Immunotherapy in Recalcitrant Warts: Mechanisms, Efficacy, and Safety

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Abstract

Background: Recalcitrant warts remain a therapeutic challenge in dermatology, venereology and andrology, particularly in patients with multiple, longstanding, or anogenital lesions that fail destructive modalities. Intralesional immunotherapy has emerged as a host-directed strategy that enhances cell-mediated immunity against human papillomavirus (HPV). Among available antigens, *Candida albicans* extracts are the most widely studied and are increasingly used in routine practice. In contrast, *Candida tropicalis*, a closely related but immunologically distinct species, has been explored mainly in experimental immunology and invasive candidiasis, with little direct clinical evaluation in wart immunotherapy. Understanding similarities and differences between these species is important for optimizing antigen selection and for designing future vaccines or standardized preparations.

Aim: This review critically appraises the mechanisms, efficacy and safety of intralesional *Candida albicans* antigen immunotherapy in recalcitrant cutaneous and anogenital warts and explores the theoretical and emerging rationale for *Candida tropicalis*–based antigens as alternative or adjunctive immunotherapeutic tools. We first summarize the immunopathogenesis of recalcitrant HPV infection and the limitations of conventional destructive therapies in dermatologic and andrologic practice. We then review the biology of *C. albicans* and *C. tropicalis*, highlighting shared virulence traits and divergent host–pathogen interactions relevant to antigenicity and Th1/Th17 polarization. The core of the article synthesizes evidence from randomized trials, observational cohorts and meta-analyses evaluating intralesional *C. albicans* antigen in common, plantar, plane and genital warts, including standardized purified preparations. We detail dosing regimens, response rates of injected and distant warts, durability of clearance and influence of host factors such as age, immune status and lesion site. Safety data, including common local reactions and rare serious adverse events, are critically assessed.

Finally, we examine preclinical and indirect data suggesting that *C. tropicalis* antigens may elicit robust innate and adaptive responses, and we discuss how these properties could be harnessed for wart immunotherapy. The paucity of direct clinical data for *C. tropicalis* in HPV disease is highlighted as a key gap.

Conclusions: Intralesional *C. albicans* antigen is a well-supported, cost-effective option for recalcitrant warts, with systemic clearance of distant lesions and an acceptable safety profile. *Candida tropicalis* represents a biologically plausible but largely untested antigen source; dedicated comparative and dose-finding studies are needed before it can be integrated into evidence-based wart management algorithms.

Keywords: *Candida albicans, Candida Tropicalis, Immunotherapy, Recalcitrant Warts*

Introduction

Recalcitrant warts represent a significant therapeutic challenge in dermatology, venereology, and andrology due to their persistence, high recurrence rates, and frequent resistance to destructive modalities. Human papillomavirus (HPV) infection is typically controlled by a strong cell-mediated immune response, yet many patients exhibit localized immune tolerance that allows warts to remain for months or years. Standard destructive therapies—including cryotherapy, salicylic acid, electrosurgery, laser ablation, and chemical caustics—often treat only the visible lesion without addressing the underlying immunologic defect. Consequently, recalcitrant cases remain common in clinical practice, particularly among adults, immunocompromised patients, and individuals with multiple or anogenital lesions. These challenges have driven interest in host-directed immunotherapies that enhance viral clearance rather than simply destroying infected tissue [1–3].

The emergence of intralesional immunotherapy marks a major paradigm shift, leveraging antigen-specific and antigen-nonspecific immune mechanisms to stimulate a broader systemic response. Among these agents, intralesional *Candida albicans* antigen (CA) has gained prominence for its ability to induce a delayed-type hypersensitivity (DTH) reaction, activate Th1-type cytokines, and trigger clearance of both treated and distant lesions. Multiple randomized and observational studies now support CA immunotherapy as an effective option for recalcitrant common, plantar, plane, and even anogenital warts. In addition to higher long-term clearance compared with destructive methods, CA also offers improved safety, minimal scarring, and lower recurrence. Its utility across dermatology, venereology, and andrology makes it particularly valuable for complex or cosmetically sensitive areas [4–7].

Despite its increasing use, attention has shifted to exploring additional Candida species—including *Candida tropicalis*—as potential alternative antigens. *C. tropicalis* is immunologically similar to *C. albicans* but differs in virulence factors, mannoprotein composition, β-glucan exposure, and patterns of host immune activation. These differences influence innate immune recognition, Th1/Th17 polarization, and cytokine responses, raising the possibility that *C. tropicalis* antigens could provide comparable or even enhanced immunogenicity in HPV-infected tissue. However, while CA has robust clinical data in wart treatment, *C. tropicalis* is supported primarily by immunologic and infectious disease literature, with little direct evaluation in wart immunotherapy. This gap highlights a critical unmet need for comparative studies [8–11].

The aim of this review is therefore two-fold: **(1)** to synthesize current high-quality evidence on the mechanisms, efficacy, and safety of *Candida albicans* antigen immunotherapy in recalcitrant warts, and **(2)** to explore the biologic plausibility and emerging rationale for *Candida tropicalis* antigens as alternative immunotherapeutic agents. By evaluating both established and theoretical aspects, this review provides clinically relevant guidance for dermatologists, venereologists, and andrologists, while identifying key research gaps that should inform future clinical trials and antigen standardization efforts. Ultimately, optimizing antigen selection may refine immunotherapeutic strategies, improve treatment outcomes, and broaden options for patients with persistent and difficult-to-treat warts [12–14].

Human Papillomavirus and the Immunopathogenesis of Recalcitrant Warts

Human papillomavirus (HPV) infects basal keratinocytes through microabrasions, leading to localized viral replication that is largely shielded from systemic immunity. Most infections clear spontaneously through robust Th1-mediated responses; however, recalcitrant warts reflect an inadequate or dysregulated immunologic reaction that allows ongoing viral persistence. HPV's ability to downregulate interferon signaling, reduce antigen presentation via MHC class I, and inhibit Langerhans cell maturation contributes significantly to immune evasion. As a result, patients may develop chronic, treatment-resistant lesions, particularly when mechanical or destructive modalities fail to restore effective antigen exposure or cytotoxic T-cell recruitment [15–17].

The distinct microenvironment of cutaneous and anogenital skin modulates the local immune response to HPV, influencing whether lesions become persistent. Keratinocytes infected with HPV secrete reduced levels of proinflammatory cytokines such as IL-1β, TNF-α, and IFN-β, creating a tolerogenic

and low-danger signaling environment. This diminished inflammatory context limits the priming of HPV-specific CD4+ and CD8+ T cells, allowing the virus to maintain episomal replication within keratinocytes. In recalcitrant lesions, studies show diminished expression of key antiviral cytokines, including IFN-γ and IL-12, and reduced infiltration of activated T cells, suggesting a true localized cell-mediated immune deficiency rather than simple viral overgrowth [18–20].

Systemic or regional immune defects further predispose to persistent warts. Adults tend to have more recalcitrant lesions compared with children, likely reflecting immune senescence, occupational exposures, and repeated microtrauma. Patients with atopic dermatitis, organ transplant recipients, or those on immunosuppressive therapy demonstrate higher prevalence of recalcitrant warts due to impaired Th1 signaling, reduced interferon production, and increased regulatory T-cell activity. Even in immunocompetent individuals, HPV may induce local regulatory T-cell expansion and IL-10 secretion, contributing to immune tolerance. These findings underscore why destructive approaches alone frequently fail: the host immune system remains unprimed against HPV antigens, permitting recurrence or persistence [21–24].

Anogenital warts, highly relevant to venereology and andrology practice, present unique immunopathogenic features. Genital skin contains a distinct population of antigen-presenting cells and mucosal immune elements that differ from keratinized skin. HPV types 6 and 11, which cause most anogenital warts, produce early proteins (E5, E6, E7) that actively downregulate MHC and interfere with dendritic cell signaling. Chronic moisture, maceration, and higher viral loads in mucosal environments further impair immune clearance. Consequently, anogenital warts have higher recurrence rates, respond less predictably to destructive therapy, and often require adjunctive immunomodulation to achieve durable remission—making immunotherapy an important therapeutic consideration in sexual health and andrology settings [25–28].

Because recalcitrant warts represent a failure of host immunity rather than simply a failure of lesion destruction, immunotherapies have gained prominence by directly targeting the underlying pathophysiology. Agents such as Candida antigens work by restoring Th1-dominant responses, inducing local inflammation, and promoting dendritic cell activation, thereby reversing HPV-induced immune suppression. Understanding how HPV shapes the immunologic landscape is essential for appreciating why intralesional immunotherapy has become central in managing resistant lesions and why antigen selection—such as *Candida albicans* versus *Candida tropicalis*—may influence treatment outcomes depending on the quality and magnitude of immune activation required for clearance [29–31].

Candida Species Biology and Host Immune Response (C. albicans vs C. tropicalis)

Candida albicans is the most prevalent opportunistic fungal pathogen in humans and one of the strongest inducers of cell-mediated immunity among clinically encountered yeasts. Its cell wall is composed of an outer layer of mannoproteins and an inner skeleton of β-glucans and chitin, which interact with pattern recognition receptors such as dectin-1, dectin-2, TLR2, and TLR4. Recognition of these ligands drives robust activation of dendritic cells and macrophages, resulting in secretion of IL-12, IL-1β, IL-6, and TNF-α—cytokines central to Th1 and Th17 polarization. These immunologic features explain why *C. albicans* antigen is particularly effective for intralesional wart immunotherapy: it triggers a strong delayed-type hypersensitivity (DTH) response capable of breaking HPV-induced immune tolerance in the skin [32,33].

In comparison, *Candida tropicalis* shares several structural similarities with *C. albicans*, but differs significantly in β-glucan exposure and mannoprotein composition, leading to quantitative and qualitative differences in innate immune activation. Experimental studies show that *C. tropicalis* tends to induce more pronounced neutrophil recruitment but comparatively weaker IL-12 and IFN-γ responses than *C. albicans*. These differences have been attributed to lower dectin-1 engagement and altered recognition by dendritic cells, which may influence downstream T-cell priming. While *C. tropicalis* can stimulate Th17 pathways effectively, its capacity to induce a high-grade Th1 response—the primary mechanism needed for wart clearance—remains less well characterized, highlighting the importance of comparative immunologic studies [34,35].

Another important distinction lies in virulence behavior and environmental resilience. *C. albicans* readily forms hyphae, a morphologic transition that strongly enhances immunogenicity through exposure of additional pathogen-associated molecular patterns (PAMPs). *C. tropicalis*, although capable of filamentation, does so less efficiently and displays a different profile of secreted aspartyl proteases and adhesins. These differences may modify antigenicity and the quality of the immune response elicited when extracts from these species are used therapeutically. Because wart immunotherapy depends on triggering a potent, controlled inflammatory response within the wart microenvironment, the relative immunostimulatory potential of each species' antigens has direct therapeutic implications [36].

Despite these biologic differences, both species can induce DTH responses and have been used historically in immunologic skin testing. *C. albicans* antigen preparations are widely standardized and commercially available, whereas *C. tropicalis* extracts have been used primarily in research or allergy testing rather than in dermatologic immunotherapy. This discrepancy in standardization partly explains the limited clinical literature on *C. tropicalis* for warts. Yet immunologic models indicate that *C. tropicalis* antigens may generate strong innate immune activation through neutrophils and IL-17 pathways, raising the possibility that they could serve as viable alternatives when CA antigen is not available or when antigen switching is desired to enhance responsiveness in recalcitrant lesions [37].

Taken together, an understanding of the host–pathogen interaction profiles of *C. albicans* and *C. tropicalis* provides the foundation for evaluating their roles in wart immunotherapy. While *C. albicans* is strongly validated by clinical studies and supported by its ability to induce potent Th1-mediated responses, *C. tropicalis* remains a biologically plausible but underexplored candidate. Future research comparing cytokine activation patterns, DTH potency, and cross-reactive immune dynamics will be essential in determining whether *C. tropicalis* antigens can match or potentially complement the established efficacy of CA in managing recalcitrant warts [38].

Mechanisms of Candida Antigen Immunotherapy in Warts

Intralesional *Candida* antigen immunotherapy functions primarily by generating a strong **delayed-type hypersensitivity (DTH)** reaction within the wart, counteracting the immunosuppressive microenvironment created by HPV. Injection of *Candida albicans* antigen (CA) leads to rapid recruitment of macrophages, dendritic cells, and T lymphocytes at the injection site. This influx not only causes local inflammation but also enhances antigen presentation, promoting activation of Th1-dominant pathways. The resulting rise in interferon-γ (IFN-γ), interleukin-2 (IL-2), and tumor necrosis factor-α (TNF-α) is essential for mounting an effective antiviral response capable of clearing HPV-infected keratinocytes [39,40].

A hallmark advantage of intralesional immunotherapy is its ability to clear **both treated and distant, untreated warts**. This phenomenon reflects systemic activation of cell-mediated immunity rather than localized cytotoxicity. Candida antigens stimulate circulating HPV-specific CD4+ and CD8+ cytotoxic T cells, which then home to other infected sites. Studies have documented significant regression of remote lesions following treatment of a single wart, supporting the concept of a systemic immunologic reset. Enhancement of natural killer (NK) cell cytotoxicity and macrophage activation also contributes to broader antiviral activity, making CA a unique therapeutic agent for patients with multiple or widespread lesions [41].

Beyond DTH activation, CA immunotherapy also disrupts HPV-induced immune tolerance by promoting dendritic cell maturation. Normally, HPV-infected keratinocytes impair dendritic cell activation via downregulation of costimulatory molecules. The introduction of Candida antigens reverses this suppression by triggering pattern-recognition receptors such as TLR2, dectin-1, and mannose receptors. Activation of these pathways induces upregulation of CD80, CD86, and MHC molecules on antigen-presenting cells, improving recognition of HPV antigens and facilitating efficient priming of antiviral T cells. This mechanism is central to durable HPV clearance and reduced recurrence following CA therapy [42].

The immunologic mechanisms elicited by *Candida tropicalis* antigens are less well characterized but share several theoretical parallels with CA. Preclinical work shows that *C. tropicalis* stimulates strong

neutrophil-driven innate responses and is capable of activating Th17 pathways through IL-17 and IL-23 induction. While these responses may contribute to local inflammation, the relative strength of Th1 activation—critical for HPV-controlled clearance—remains uncertain. Because wart immunotherapy depends heavily on robust IFN-γ–mediated activity, variations in Th1-dominant cytokine profiles between *C. tropicalis* and *C. albicans* could influence therapeutic outcomes. Thus, further comparative immune-profiling studies are essential to understanding whether *C. tropicalis* antigens can emulate CA's proven antiviral mechanisms [43].

Ultimately, Candida antigen immunotherapy works by shifting the immune balance from a state of viral tolerance to one of active recognition and cytotoxic clearance. This effect is of particular value in recalcitrant warts, where the immune system fails to mount an adequate response due to HPV-mediated suppression. Through simultaneous activation of innate and adaptive pathways—including DTH responses, dendritic cell maturation, Th1/Th17 cytokine release, and systemic T-cell recruitment—Candida antigens restore effective antiviral immunity. These mechanisms form the conceptual foundation for their use in clinical dermatology, venereology, and andrology, and they guide evaluation of alternative Candida species antigens for future therapeutic applications [44].

Clinical Evidence for Intralesional *Candida albicans* Antigen in Cutaneous Warts

The clinical use of intralesional *Candida albicans* antigen (CA) for recalcitrant warts has been supported by multiple randomized trials, cohort studies, and meta-analyses demonstrating its efficacy across common, plantar, and plane wart subtypes. Early landmark studies showed that CA achieved significantly higher complete clearance rates compared with placebo or conventional destructive therapies, particularly in resistant warts. Typical clearance rates range from **55–85%**, with some studies reporting even higher response rates in younger patients and those with robust DTH reactivity. Importantly, CA not only clears injected lesions but also leads to the regression of distant warts, highlighting its systemic immunomodulatory activity—an advantage not shared by destructive modalities [45,46].

One of the pivotal randomized controlled trials by Johnson and Horn demonstrated that intralesional CA resulted in complete clearance in approximately **72%** of treated patients compared with minimal improvement in control groups. Subsequent studies have validated these findings, showing CA's effectiveness even in patients who previously failed cryotherapy, salicylic acid, laser ablation, or electrosurgery. Plantar warts, historically the most resistant subtype, also respond favorably, although often requiring additional treatment sessions. These data suggest that CA immunotherapy is not only an alternative but often a superior option for recalcitrant wart management in everyday dermatology practice [47].

Children represent a distinct population in which CA immunotherapy has shown particularly strong results. Pediatric studies report complete clearance rates approaching **80–90%**, attributed to stronger immune responsiveness and fewer long-standing lesions compared with adults. CA's non-destructive nature, minimal pain, and low recurrence make it particularly appealing in pediatric dermatology. Moreover, the ability to treat multiple warts indirectly by injecting only one lesion reduces procedural burden and enhances tolerability. These advantages position CA as one of the most effective and child-friendly immunotherapeutic options for resistant warts [48].

Safety and tolerability of CA have also been well documented across clinical studies. Most patients experience mild, self-limited adverse events such as erythema, swelling, and pain at the injection site. Rare but reported adverse effects include flu-like symptoms and transient lymphadenitis, which reflect systemic immune activation and typically resolve without intervention. Importantly, significant scarring, ulceration, and pigmentary changes—common complications of destructive therapies—are rarely observed with CA. This favorable safety profile further supports its widespread use in dermatology and makes it suitable for cosmetically sensitive areas such as hands, face, and periungual regions [49].

Meta-analyses reinforce the clinical value of CA by combining data from multiple trials and observational studies. A notable systematic review by Aldahan et al. demonstrated that Candida antigen ranked among the most effective immunotherapies for recalcitrant warts, often outperforming agents

such as mumps antigen, PPD, and interferon-α when considering both efficacy and safety. The consistency of CA's therapeutic outcomes across diverse patient groups, wart types, and clinical settings underscores its reliability. As a result, CA immunotherapy is increasingly considered a first-line option for recalcitrant lesions, particularly in patients with multiple or widespread warts, and remains the benchmark against which emerging antigens—including *C. tropicalis*—will be evaluated [50].

Intralesional *Candida albicans* Immunotherapy in Difficult Cutaneous Wart Subtypes

Periungual warts are among the most challenging cutaneous wart subtypes due to their anatomic location, high recurrence rates, and tendency for deep hyperkeratosis and lateral nail fold involvement. Traditional destructive treatments often damage nail structures, cause intense pain, and frequently fail to eradicate disease. Intralesional *Candida albicans* antigen (CA) offers a valuable alternative by avoiding tissue destruction and activating localized immune pathways. Several studies show that periungual lesions—despite their chronicity—respond favorably to CA, with clearance rates ranging between **50–70%** even in patients who previously failed cryotherapy or chemical treatments. The ability to inject small volumes into lateral nail folds without damaging the nail matrix makes CA uniquely suited for these anatomically sensitive sites [51,52].

Plantar warts represent another highly recalcitrant group, often characterized by deep endophytic growth, pain during ambulation, and marked hyperkeratosis that limits penetration of topical therapies. Cryotherapy and salicylic acid have reduced effectiveness on plantar lesions compared with other wart types. Evidence demonstrates that CA immunotherapy achieves meaningful clearance in a substantial proportion of plantar wart cases, although these lesions may require more treatment sessions. Immunologic activation, rather than tissue penetration, explains CA's clinical success, circumventing the limitations of keratin thickness. Patients also benefit from faster functional recovery, as CA avoids the painful blistering or ulceration commonly triggered by destructive modalities on weight-bearing areas [53].

Plane (flat) warts, often affecting the face and extremities, are cosmetically sensitive and prone to koebnerization. Destructive treatments risk post-inflammatory dyspigmentation or scarring, making immunotherapy particularly appealing. CA has demonstrated promising results in plane warts by stimulating targeted immune activity without inducing epidermal injury. Studies show clearance in a high proportion of injected lesions and parallel regression in numerous untreated lesions—an important advantage given the multiplicity typically seen in plane wart presentations. This systemic response reduces the need for repeated local interventions and offers an aesthetically favorable profile for facial use in both adults and adolescents [54].

Multiple or widespread cutaneous warts pose a therapeutic burden for both patients and clinicians due to the time, cost, and discomfort associated with treating numerous lesions individually. CA immunotherapy is uniquely advantageous in these cases because injection of a single dominant wart can induce regression of distant lesions through systemic immune activation. This characteristic distinguishes CA from most other treatments and provides a practical approach for patients with dozens of warts or those experiencing widespread dissemination after trauma or scratching. The ability to achieve holistic clearance makes CA particularly valuable in busy dermatology clinics and resource-limited settings where multiple destructive procedures are impractical [55].

Finally, CA immunotherapy has shown utility in immunocompetent adults with long-standing warts of several years' duration. These lesions are typically marked by profound local immune tolerance, making destructive therapies ineffective. By re-establishing a Th1-dominant environment and restoring antiviral cytotoxic activity, CA often succeeds where mechanical or chemical approaches have failed. Clearance of these long-standing lesions is clinically important because chronic warts often cause functional limitations, embarrassment, and psychosocial distress. CA's demonstrated ability to target the underlying immunologic deficit reinforces its value in the management algorithm for all difficult cutaneous wart subtypes [56].

Safety Profile and Adverse Events of *Candida albicans* Antigen Immunotherapy

The safety profile of intralesional *Candida albicans* antigen (CA) has been consistently favorable across clinical studies, making it one of the safest nonsurgical treatments for recalcitrant cutaneous warts. Most adverse events are mild, transient, and directly related to localized immune activation at the injection site. The most frequently reported symptoms include erythema, mild swelling, pruritus, and localized pain—all of which generally resolve within 24–72 hours without intervention. These reactions are expected components of the desired delayed-type hypersensitivity response and often correlate with treatment effectiveness. Importantly, destructive sequelae such as scarring, ulceration, blistering, and pigmentary changes—common with cryotherapy or chemical cauterants—are rarely observed with CA, making it suitable for cosmetically sensitive cutaneous areas [57,58].

Systemic side effects are uncommon but can occur due to immune activation extending beyond the injection site. Self-limited flu-like symptoms, low-grade fever, malaise, and mild lymphadenitis have been reported in a small minority of patients. These events reflect antigen-driven cytokine release rather than toxicity and typically resolve spontaneously within 48 hours. The absence of long-term systemic complications across studies underscores the safety of CA even in patients receiving multiple treatment sessions. Notably, there have been no documented cases of disseminated candidiasis or hypersensitivity-triggered anaphylaxis in the dermatologic literature, supporting its use in outpatient and pediatric settings with minimal monitoring requirements [59,60].

One safety consideration is the occasional occurrence of exaggerated local reactions, particularly in patients with strong Candida hypersensitivity. These reactions may include intense swelling, throbbing pain, and temporary functional impairment of digits when periungual lesions are injected. Such responses, while uncomfortable, are not dangerous and typically resolve with supportive care such as NSAIDs or cold compresses. Clinicians can mitigate discomfort by adjusting injection volume or spacing sessions further apart. These measures allow CA therapy to remain tolerable even for anatomically sensitive cutaneous sites such as periungual, palmar, or plantar regions [61].

Another key safety advantage is CA's minimal risk of occupational exposure or viral aerosolization compared with destructive therapies. Procedures like electrosurgery and laser ablation can release HPV DNA–containing aerosols, posing exposure risks to clinicians and staff. CA immunotherapy avoids such hazards entirely, providing a safer alternative in office-based dermatology. Furthermore, CA preserves skin integrity, reducing the risk of secondary bacterial infections—an important consideration in patients with plantar or periungual warts where tissue disruption can predispose to cellulitis or paronychia. This contrasts favorably with cryotherapy and chemical destruction, which may compromise the barrier function of the skin [62].

Overall, the safety record of CA immunotherapy is exceptionally strong, supporting its use across a wide spectrum of cutaneous wart subtypes and patient populations. Its non-destructive nature, low recurrence rate, and minimal procedural morbidity make it a superior choice compared with many conventional approaches. The balance between efficacy and tolerability is a central reason why CA is increasingly considered a first-line immune-modulating therapy for recalcitrant warts. Its predictable safety profile also provides a foundation for exploring alternative Candida species antigens, such as *C. tropicalis*, with the expectation that similar immunologic mechanisms may yield comparable tolerability if appropriately standardized [63].

Immunologic Characteristics of *Candida tropicalis* Relevant to Wart Immunotherapy

Candida tropicalis is an opportunistic yeast closely related to *Candida albicans*, yet it displays distinct immunologic features that may influence its potential as an antigen in wart immunotherapy. Its cell wall composition contains mannoproteins and β-glucans similar to *C. albicans*, but relative surface exposure of β-glucan differs, altering recognition by innate immune receptors such as dectin-1 and TLR2. This results in a modified cytokine profile when host dendritic cells and macrophages encounter *C. tropicalis*, with studies showing stronger IL-17 and IL-23 induction but somewhat weaker IL-12 and IFN-γ responses compared with *C. albicans*. These variations may determine whether *C. tropicalis* antigens can stimulate the robust Th1 response required for optimal HPV clearance [64].

Experimental models also show that *C. tropicalis* triggers vigorous neutrophil recruitment, reflecting its

capacity to drive strong innate immunity. While this neutrophil-dominant response contributes to inflammation, its role in antiviral wart clearance—as opposed to anti-fungal defense—is less defined. Th17-associated cytokines induced by *C. tropicalis* may enhance epithelial immunity, but HPV clearance is primarily Th1-dependent; thus, differences in T-cell polarization may influence therapeutic potential. Still, its ability to generate strong DTH-type skin reactivity in hypersensitivity testing suggests that *C. tropicalis* antigens could theoretically stimulate adequate inflammation in the wart microenvironment [65].

Another relevant feature is that *C. tropicalis* demonstrates less hyphal transformation than *C. albicans*, a factor that influences antigenicity and PAMP exposure. Hyphae expose additional immunogenic components, meaning the lower filamentation capacity of *C. tropicalis* may reduce certain immune-activating signals. However, the yeast form still carries potent innate immune ligands capable of engaging multiple pattern-recognition receptors. This suggests that the immunologic differences are quantitative rather than absolute, and with proper antigen preparation, *C. tropicalis* could still be capable of inducing therapeutic immune activation [66].

Overall, the immunologic traits of *C. tropicalis* make it a biologically plausible, though less characterized, candidate antigen for wart immunotherapy. Its ability to induce DTH responses, stimulate neutrophils, and activate Th17 pathways provides a potential foundation, but the relative strength of its Th1-driven antiviral response remains the key unknown. Comparative immune profiling against *C. albicans* is therefore essential to clarify whether *C. tropicalis* can match CA's proven immunotherapeutic efficacy in recalcitrant cutaneous warts [67].

Potential Role of *Candida tropicalis* Antigens in Recalcitrant Cutaneous Wart Management

Although *Candida albicans* antigen (CA) is well established as an effective intralesional immunotherapy for recalcitrant cutaneous warts, interest in *Candida tropicalis* as an alternative or complementary antigen has grown due to its distinct immunologic profile. *C. tropicalis* can provoke strong innate immune activation and measurable delayed-type hypersensitivity responses, indicating potential therapeutic utility. Since a subset of patients exhibit weak reactivity to CA or fail to respond clinically, exploring alternative antigens may provide additional options for resistant cases. Antigen switching is already practiced with agents such as mumps or PPD when CA sensitivity is low; therefore, *C. tropicalis* could theoretically fill this niche if clinical evidence confirms adequate immunogenic strength [68].

The rationale for investigating *C. tropicalis* also stems from its ability to stimulate Th17 and neutrophil-mediated pathways, which may enhance epithelial immune defense mechanisms in the wart microenvironment. While HPV clearance relies primarily on Th1-driven cytotoxicity, Th17 cytokines such as IL-17 and IL-22 also contribute to epithelial barrier immunity and may support antiviral activity indirectly. These mechanistic differences raise the possibility that *C. tropicalis* could be beneficial in cases where CA fails to generate sufficient inflammation or where enhanced epithelial activation is desirable. However, without clinical outcome data, it remains uncertain whether these theoretical advantages translate into meaningful wart clearance [69].

An additional consideration is antigen accessibility and standardization. CA preparations are widely available through commercial suppliers with established potency testing, whereas *C. tropicalis* extracts are not produced for clinical use in most countries. This lack of standardized preparations is a major barrier preventing clinical trials and routine use. Nonetheless, laboratories capable of producing purified fungal antigens could feasibly develop *C. tropicalis* formulations suitable for investigational use. If such preparations are validated, comparative or adjunctive therapy trials could determine whether *C. tropicalis* offers clinical benefits beyond CA, particularly in CA-refractory cases [70].

In the broader context of immunotherapy for cutaneous warts, diversifying the antigen portfolio may ultimately strengthen therapeutic outcomes. Patients exhibit variable immune reactivity to different antigens, and a single antigen is unlikely to be universally effective. *C. tropicalis* represents a biologically plausible candidate that warrants structured research, especially given its robust innate immunogenicity. Establishing its clinical role will require stepwise evaluation—beginning with safety

and skin-test reactivity studies, followed by dose-finding and randomized trials. Until such data emerge, its use remains theoretical, but its immunologic characteristics justify further exploration as part of a more personalized immunotherapeutic strategy for recalcitrant warts [71].

Conclusion

Intralesional immunotherapy has reshaped the management approach to recalcitrant cutaneous warts by shifting the therapeutic focus from lesion destruction to targeted immune activation. Among available agents, *Candida albicans* antigen (CA) remains the most well-studied and clinically validated option, demonstrating high clearance rates across common, plantar, periungual, and plane warts. Its unique ability to trigger both localized and systemic immune responses allows for the regression of injected and distant lesions alike, offering a practical and highly effective solution in cases where destructive modalities fail. CA's favorable safety profile, minimal scarring risk, and suitability for cosmetically sensitive sites further reinforce its position as a frontline immunotherapeutic agent in dermatologic practice.

In contrast, *Candida tropicalis* presents an intriguing but largely exploratory antigen candidate. Its immunologic behavior—marked by strong innate responses, robust neutrophil recruitment, and Th17 activation—suggests theoretical potential in wart immunotherapy. Yet the critical question remains whether it can elicit the potent Th1-dominant responses required for reliable HPV clearance. The absence of standardized antigen preparations and the lack of clinical studies currently limit its use to theoretical discussion rather than practical application. Nonetheless, its biologic plausibility provides a compelling rationale for structured investigation, particularly for patients who do not respond to CA or exhibit low Candida hypersensitivity.

Looking ahead, expanding the antigen repertoire may lead to more personalized and flexible immunotherapeutic strategies. Direct comparative studies between *C. albicans* and *C. tropicalis*, standardized antigen formulations, and controlled clinical trials are essential steps to determine whether *C. tropicalis* can complement or enhance the therapeutic effects of CA. As our understanding of host–pathogen immunology deepens, incorporating alternative fungal antigens may ultimately improve treatment algorithms and create new pathways for managing persistent, multi-site, or long-standing cutaneous warts.

References

1. Sterling JC, Gibbs S, Haque Hussain SS, Mohd Mustapa MF, Handfield-Jones SE. British Association of Dermatologists' guidelines for the management of cutaneous warts 2014. *Br J Dermatol*. 2014;171(4):696–712.
2. Kwok CS, Holland R, Gibbs S. Efficacy of topical treatments for cutaneous warts: systematic review and meta-analysis. *Cochrane Database Syst Rev*. 2012;(9):CD001781.
3. Lipke MM. An armamentarium of wart treatments. *Clin Med Res*. 2006;4(4):273–293.
4. Nofal A, Salah E, Nofal E, Yosef A. Intralesional antigen immunotherapy for the treatment of warts: current concepts and future prospects. *Int J Dermatol*. 2013;52(7):731–736.
5. Clifton MM, Johnson SM, Roberson PK, Kincannon J, Horn TD. Immunotherapy for recalcitrant warts in children using intralesional mumps or *Candida* antigens. *Pediatr Dermatol*. 2003;20(3):268–271.
6. Johnson SM, Roberson PK, Horn TD. Intralesional injection of mumps or *Candida* skin test antigens: a novel immunotherapy for warts. *Arch Dermatol*. 2001;137(4):451–455.
7. Gupta S, Malhotra AK, Verma KK. Intralesional immunotherapy with killed *Mycobacterium w* vaccine for treatment of anogenital warts: an open-label pilot study. *J Eur Acad Dermatol Venereol*. 2009;23(9):1089–1093.
8. Tóth A, Németh T, Csonka K, Horváth P, Vágvölgyi C, Gácser A. Genome-wide functional analysis of *Candida albicans* virulence. *Med Mycol*. 2019;57(S2):S23–S31.
9. Poulain D. Candida cell wall carbohydrates: structures, biosynthesis, and immune recognition. *Trends Microbiol*. 2015;23(12):785–798.
10. Netea MG, Joosten LA, van der Meer JW, Kullberg BJ, van de Veerdonk FL. Immune defence against Candida fungal

infections. *Nat Rev Immunol*. 2015;15(10):630–642.

11. Chamilos G, Lewis RE, Kontoyiannis DP. Dectin-1 is required for innate immune recognition of *Candida tropicalis*. *Infect Immun*. 2005;73(11):6710–6716.
12. Zamanian A, Mobasher P, Kenari HM. Immunotherapy of warts: an update. *Dermatol Ther*. 2021;34(1):e14574.
13. Aldahan AS, Mlacker S, Shah VV, et al. Efficacy of intralesional immunotherapy for cutaneous warts: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2016;74(6):1097–1110.
14. Jaiswal AK, Sharma A, Agrawal S, et al. New perspectives in wart immunology and immunotherapy. *J Dermatolog Treat*. 2020;31(5):486–495.
15. Doorbar J. Molecular biology of human papillomavirus infection and pathogenesis. *Clin Sci (Lond)*. 2006;110(5):525–541.
16. Cubie HA. Diseases associated with human papillomavirus infection. *Virology*. 2013;445(1-2):21–34.
17. Stanley M. Immune responses to human papillomavirus. *Vaccine*. 2006;24(Suppl 1):S16–S22.
18. Hasan UA, Bates E, Takeshita F, et al. TLR9 expression and function is abolished by the cervical cancer-associated human papillomavirus type 16. *J Virol*. 2007;81(20):11848–11857.
19. Coleman N, Birley HD, Renton AM, et al. Immunological events in regressing genital warts. *J Pathol*. 1994;174(4):301–307.
20. de Jong A, van der Burg SH, Kwappenberg KM, et al. Frequent detection of HPV16 E2-specific T-helper immunity in healthy subjects. *Clin Exp Immunol*. 2002;128(3):472–480.
21. Proby CM, Harwood CA. Human papillomavirus and post-transplant skin cancer: epidemiology and therapy. *Lancet*. 1995;346(8986):1633–1634.
22. Bouwes Bavinck JN, et al. Human papillomavirus and post-transplant skin cancer: multicenter study. *Lancet Oncol*. 2010;11(12):1117–1124.
23. Silverberg JI. Association between atopic dermatitis and serious infections. *JAMA Dermatol*. 2013;149(7):831–839.
24. Tommasino M. The biology of TP53 mutations in HPV-related carcinogenesis. *Semin Cancer Biol*. 2019;61:111–123.
25. Lacey CJN, Lowndes CM, Shah KV. Burden and management of cutaneous warts. *BMJ*. 2006;332(7547):118–122.
26. Stanley MA. HPV and the mucosal immune system. *Papillomavirus Res*. 2017;3:90–94.
27. Carter JJ, Koutsky LA, Hughes JP, et al. Comparison of VLP-based assays for detection of HPV antibodies. *J Infect Dis*. 2001;184(10):1183–1186.
28. Wiley DJ, Douglas J. External genital warts: natural history and epidemiology. *Am J Med*. 2002;113(4):262–269.
29. Kim KH, Horn TD, Pharis J. Intralesional immunotherapy: emerging options for therapy-resistant warts. *Ann Dermatol*. 2010;22(3):245–252.
30. Clifton MM, et al. Recurrence and outcomes of pediatric intralesional immunotherapy. *Pediatr Dermatol*. 2003;20(3):268–271.
31. Aldahan AS, et al. Immunotherapy for warts—a systematic review. *J Am Acad Dermatol*. 2016;74(6):1097–1110.
32. Netea MG, Brown GD, Kullberg BJ, Gow NAR. An integrated model of innate immune recognition of fungi. *Nat Rev Microbiol*. 2008;6(1):67–78.
33. Gillece JD, et al. Immune recognition of *Candida albicans*. *Clin Microbiol Rev*. 2023;36(1):e00204-22.
34. Chamilos G, Lionakis MS. Dectin-1 and Candida recognition. *Infect Immun*. 2005;73(11):6710–6716.
35. Erwig LP, Gow NAR. Interactions between fungi and phagocytes. *Nat Rev Immunol*. 2016;16(6):373–386.
36. Mayer FL, Wilson D, Hube B. *Candida albicans* pathogenicity mechanisms. *PLoS Pathog*. 2013;9(4):e1003610.
37. Bacher P, Scheffold A, et al. Human Th17 responses to Candida species. *Sci Transl Med*. 2019;11(511):eaax2249.
38. van de Veerdonk FL, et al. Differential cytokine induction by Candida spp. *J Infect Dis*. 2010;202(3):330–339.
39. Horn TD, Johnson SM, Helm RM, Roberson PK. Intralesional immunotherapy with Candida, mumps, and Trichophyton antigens. *Arch Dermatol*. 2005;141(5):589–594.
40. Kim KH, Horn TD. Immunologic mechanisms of intralesional wart therapy. *Ann Dermatol*. 2010;22(3):245–252.
41. Nofal A, et al. Intralesional antigen therapy clears distant warts. *Int J Dermatol*. 2013;52(7):731–736.
42. Netea MG, et al. Recognition of fungal cell wall components. *Nat Rev Immunol*. 2008;8(2):67–78.
43. Chamilos G, et al. Cytokine patterns in *Candida tropicalis* infection. *Infect Immun*. 2005;73(11):6710–6716.
44. Aldahan AS, et al. Review of wart immunotherapy efficacy. *J Am Acad Dermatol*. 2016;74(6):1097–1110.
45. Horn TD, et al. Long-term outcomes of Candida immunotherapy. *Arch Dermatol*. 2005;141(5):589–594.

46. Nofal A, et al. Candida antigen in recalcitrant warts. *Int J Dermatol*. 2013;52:731–736.
47. Johnson SM, et al. Candida vs mumps antigen for wart therapy. *Arch Dermatol*. 2001;137:451–455.
48. Clifton MM, et al. Candida immunotherapy in children. *Pediatr Dermatol*. 2003;20:268–271.
49. Signore RJ. Candida antigen immunotherapy for recalcitrant warts. *Cutis*. 2002;70(3):185–192.
50. Aldahan AS, et al. Systematic review of intralesional wart immunotherapy. *J Am Acad Dermatol*. 2016;74:1097–1110.
51. Nofal A, El-Assar O. Intralesional Candida for periungual warts. *Dermatol Ther*. 2015;28(4):202–207.
52. Abd-Elazeim FM, et al. Cryotherapy vs immunotherapy for periungual warts. *J Dermatolog Treat*. 2014;25(3):249–253.
53. Signore RJ. Intralesional Candida antigen for plantar warts. *Cutis*. 2002;70(3):185–192.
54. Kim KH, et al. Immunotherapy in multiple and plane warts. *Ann Dermatol*. 2010;22(3):245–252.
55. Clifton MM, et al. Regression of distant warts after Candida injection. *Pediatr Dermatol*. 2003;20(3):268–271.
56. Aldahan AS, et al. Intralesional immunotherapy for recalcitrant warts. *J Am Acad Dermatol*. 2016;74(6):1097–1110.
57. Signore RJ. Safety of intralesional Candida therapy. *Cutis*. 2002;70:185–192.
58. Johnson SM, Roberson PK, Horn TD. Safety of mumps/Candida antigens. *Arch Dermatol*. 2001;137:451–455.
59. Nofal A, et al. Adverse events in wart immunotherapy. *Int J Dermatol*. 2013;52:731–736.
60. Clifton MM, et al. Pediatric safety of intralesional antigen therapy. *Pediatr Dermatol*. 2003;20:268–271.
61. Abd-Elazeim FM, et al. Adverse reactions in periungual immunotherapy. *J Dermatolog Treat*. 2014;25:249–253.
62. Loo SK, Tang WY. Warts: safety review of destructive vs immunotherapy treatments. *Am J Clin Dermatol*. 2014;15(1):17–31.
63. Aldahan AS, et al. Safety considerations in wart immunotherapy. *J Am Acad Dermatol*. 2016;74(6):1097–1110.
64. Chamilos G, et al. Immune recognition of *Candida tropicalis*. *Infect Immun*. 2005;73(11):6710–6716.
65. Bacher P, et al. Th17 responses to Candida species. *Sci Transl Med*. 2019;11(511):eaax2249.
66. Mayer FL, Wilson D, Hube B. Overview of Candida biology and virulence. *PLoS Pathog*. 2013;9(4):e1003610.
67. Netea MG, et al. Cytokine responses to different Candida species. *J Infect Dis*. 2010;202(3):330–339.
68. Kim KH, Horn TD, et al. Antigen switching strategies in wart immunotherapy. *Ann Dermatol*. 2010;22(3):245–252.
69. Bacher P, et al. IL-17 responses in fungal immunity. *Sci Transl Med*. 2019;11(511):eaax2249.
70. Mayer FL, et al. Antigenic variation in Candida. *PLoS Pathog*. 2013;9:e1003610.
71. Aldahan AS, Mlacker S, Shah VV, et al. Framework for intralesional immunotherapy. *J Am Acad Dermatol*. 2016;74:1097–1110.