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Research Article

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Fennel Seeds as a Natural Bridge Between Dermatology and Oncology

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Abstract

Fennel seeds, rich in bioactive compounds such as vitamins A, C, and E, chavicol, and antioxidants, have emerged as valuable agents in both dermatological care and oncology. Known for their antiseptic and anti-inflammatory properties, fennel seeds effectively address skin issues such as acne, hyperpigmentation, fine lines, and puffiness by reducing bacterial load, calming irritation, and improving skin tone. In addition to their dermatological benefits, recent research highlights their potential in oncology, particularly in melanoma, through the inhibition of nuclear factor-kappa B (NF-κB) and matrix metalloproteinase-9 (MMP-9). By disrupting these pathways via autocrine and paracrine mechanisms, fennel seeds induce apoptosis in melanoma cells and inhibit the migration of tumor-associated mesenchymal stem cells, presenting a promising approach for targeted anti-melanoma strategies. However, the application of fennel seeds in dermatology is complicated by their tendency to increase photosensitivity, amplifying susceptibility to ultraviolet-induced damage, including sunburn and photoaging. The incorporation of protective measures, such as consistent sunscreen use, is essential to counteract this risk. Research into fennel seeds' molecular interactions and therapeutic properties has the potential to unlock innovative solutions that integrate dermatology and oncology, advancing skin health and improving cancer outcomes while addressing the limitations associated with their use. By unlocking the dual potential of fennel seeds in skin rejuvenation and cancer therapy, researchers and clinicians have the opportunity to pioneer innovative treatments that merge nature's wisdom with cutting-edge science, offering new hope for improved health outcomes.

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Introduction

Skin health and oncology share a complex and multifaceted intersection, with overlapping biological processes such as aging, oxidative stress, and cancer biology forming critical areas of exploration. The skin, which is the largest organ of the human body, is not only a barrier to environmental insults but also a mirror of systemic health, reflecting changes brought about by intrinsic and extrinsic factors. Increasing interest in natural products has opened new avenues for therapeutic advancements, particularly in addressing the dual challenges of maintaining skin health and preventing cancer. These compounds, derived from a variety of sources, have shown potential to target key biological pathways, sparking interest in their integrative role across dermatological and oncological disciplines.

In particular, the application of botanical agents in medicinal practices has gained momentum, driven by their demonstrated antioxidant and anti-inflammatory properties, two key processes implicated in both skin aging and cancer progression [1]. Among these, fennel seeds (*Foeniculum vulgare*), a member of the Apiaceae family, have garnered significant attention due to their rich composition of bioactive molecules such as vitamins A, C, and E, as well as chavicol. These compounds exhibit antioxidant, anti-inflammatory, and anticancer activities, positioning fennel as a versatile agent in therapeutic interventions. Historically rooted in traditional medicine, fennel seeds serve a wide array of uses, including treatment of stomachache, chronic fever, kidney stones, and urinary disorders [2]. *Foeniculum vulgare* has also demonstrated anticancer effects in preclinical studies, showing efficacy against tumors such as lung and prostate cancers, as well as more aggressive malignancies [3,4]. This dual functionality positions *Foeniculum vulgare* as a promising candidate for integrative and multifactorial approaches to skincare and cancer treatment.

The overall purpose of this review is to investigate the emerging duality of *Foeniculum vulgare* seeds in promoting skin health and skin cancer. With a specific focus on their antioxidant and anti-inflammatory properties, this review aims to elucidate the mechanisms by which *Foeniculum vulgare* bioactive compounds influence skin barrier function and oxidative stress while inhibiting tumor progression. By examining the structural characteristics of fennel seed bioactive compounds and their molecular targets in dermatology and oncology, particularly in relation to melanoma, this review delves into the current findings and research that is unveiling the skin-rejuvenating and anti-cancer properties of fennel seeds, highlighting the potential

influence this molecule may have as a therapeutic and implementation in dermatologic and oncologic practice.

Structural Characteristics of Bioactive Compounds

Fennel seeds are rich in bioactive compounds, each contributing to their therapeutic potential at the intersection of dermatology and oncology. Phenolic compounds, terpenes, and vitamins A, C, and E form the basis of their antioxidant, anti-inflammatory, and antimicrobial properties. These compounds interact intricately with cellular pathways, enhancing their ability to promote skin health and combat oncogenic processes.

Phenolic Compounds and Terpenes

Estragole, chavicol, anethole, and fenchone are among the primary phenolic and terpenoid compounds found in fennel. Estragole, a naturally occurring phenylpropanoid, plays a pivotal role in modulating inflammatory and oxidative pathways by neutralizing reactive oxygen species (ROS), mitigating cellular damage, and influencing transcription factors such as NF-κB [5]. Its molecular structure consists of a benzene ring substituted with a methoxy group (–OCH_3) and an allyl group. This structure contributes to its biological activity and ability to interact with cellular pathways as an antioxidizing agent. By donating electrons to ROS, estragole neutralizes ROS, preventing oxidative damage from cellular components like lipids, proteins, and DNA. Estragole also inhibits the activity of matrix metalloproteinases (MMPs), particularly MMP-9, which is involved in tumor invasion, metastasis, and skin matrix degradation, thereby preserving extracellular matrix integrity, reducing tumor spread, and calming skin irritation [6]. Its anti-inflammatory properties and ability to inhibit enzymes like MMPs make estragole a potential agent for improving skin tone by calming irritation and reducing tumor metastasis.

Chavicol, another key compound, exhibits multifaceted bioactivity, including antioxidant, antimicrobial, and anti-inflammatory properties. Its structure consists of a benzene ring substituted with a propenyl group and hydroxyl group (-OH), contributing to its ability to interact with microbial cells and disrupt their physiological processes. As a phenolic molecule, chavicol facilitates ROS scavenging by donating hydrogen atoms to neutralize free radicals, alleviating oxidative stress that contributes to cellular damage and photoaging [7]. Its antimicrobial properties stem from its ability to disrupt bacterial cell membranes, increase permeability, and cause bacterial lysis [8]. Notably, its derivative hydroxychavicol enhances these effects by preventing bacterial cell wall synthesis, reducing biofilm formation, and inducing bacterial lysis through ROS generation, further showcasing chavicol's role in preventing skin infections and promoting overall skin health. Chavicol also demonstrates anti-inflammatory effects by downregulating cyclooxygenase-2 (COX-2) expression, a key promoter of inflammatory pathways [9]. By reducing COX-2 activity, chavicol effectively reduces the production of pro-inflammatory mediators, which exacerbate skin irritation and inflammation. Chavicol is a versatile phenolic compound that effectively neutralizes oxidative stress, disrupts bacterial cell processes, and modulates inflammatory pathways to support skin health.

Anethole and fenchone, bioactive compounds found in the essential oils of fennel seeds, exhibit several biochemical properties that contribute to their therapeutic potential in dermatology and oncology alike. By integrating into the mitochondrial membrane of cancer cells, anethole induces apoptosis and inhibits cell proliferation and migration through a cascade of introducing mitochondrial dysfunction. Anethole destabilizes structural integrity by disrupting the mitochondrial membrane potential and promotes apoptosis through the inhibition of anti-apoptotic signals and upregulation of apoptogenic factors, including cytochrome c. Additionally, anethole induces excessive ROS generation within the mitochondria, exacerbating oxidative stress and triggering intrinsic apoptotic pathways, inhibiting neoplastic proliferation [10]. Meanwhile, fenchone displays dose-dependent antimicrobial properties, particularly against gram-negative bacteria such as *Escherichia coli*. By reducing biofilm production in pathogens like *Pseudomonas aeruginosa* and *Candida albicans*, fenchone demonstrates its utility in addressing persistent infections [11]. The synergistic antimicrobial effects between chavicol and fenchone suggest the potential of fennel seeds as an effective promoter of skin health through bacterial modulation and prevention of skin infections.

Vitamins and Antioxidant Network

Vitamins A, C, and E form an intricate antioxidant network within fennel seeds, protecting cellular structures from oxidative damage. Vitamin C plays a crucial role in collagen synthesis as a cofactor for the enzymes prolyl hydroxylase and lysyl hydroxylase, which hydroxylate proline and lysine residues to form stable collagen structures. Additionally, vitamin C influences epigenetics by promoting collagen gene expression in fibroblasts [12,13]. With age, collagen–a protein that provides elasticity, strength, and structure to the skin–decreases, making it a popular ingredient in anti-aging skin serums. Beyond its role in collagen synthesis, vitamin C aids in the antioxidant defense system, working alongside vitamins A and E to protect cells from oxidative damage. Vitamin E, particularly α-tocopherol, stabilizes cell membranes by neutralizing ROS that initiate lipid peroxidation, protecting polyunsaturated fatty acids (PUFAs) from oxidative damage [14]. Vitamin A complements this system by scavenging ROS within cells and stabilizing membranes, enhancing the protective effects of vitamins C and E. PUFAs, particularly linoleic acid, are essential lipid molecules that contribute to the integrity of the skin's hydrophobic barrier [15]. PUFAs also exhibit anti-inflammatory and anti-tumor properties by inhibiting the lipoxygenase pathway required for tumor metastasis as well as increasing ROS within cancer cells, thereby inducing apoptosis [16]. Consequently, the preservation of PUFAs by vitamin E is imperative for maintaining skin barrier integrity and providing anti-cancer protection within the skin. The synergistic actions of vitamins A, C, and E create a robust defense system against skin aging. By promoting collagen synthesis, neutralizing oxidative damage, and maintaining the hydrophobicity of skin, these nutrients collectively combat factors that drive aging and permit carcinogenesis.

Bioavailability and Drug Delivery

The biochemical properties of fennel compounds are intricately linked to their topical bioavailability. The lipophilic nature of many fennel-derived molecules, such as chavicol and anethole, facilitates their penetration through the hydrophobic stratum corneum of the skin. However, these compounds must strike a balance between hydrophilicity and lipophilicity to cross the epidermal barrier and reach systemic circulation. Extreme lipophilic molecules may become trapped in the stratum corneum, while hydrophilic molecules may fail to penetrate the epidermis [17]. This balance is critical for optimizing drug delivery and ensuring effective cellular uptake, particularly in

formulations designed for dermatological or oncological applications.

Molecular Targets in Dermatology

Bioactivity of fennel seed phenolic compounds may offer a promising approach for treating hyperpigmentation disorders through inhibitory activity against tyrosinase, a key enzyme involved in melanin synthesis. Fennel polyphenol oxidase (PPO), an enzyme in fennel seeds known for its role in phenolic oxidation, operates within a similar enzymatic pathway to tyrosinase. Though its primary function has been studied in relation to phenolic oxidation, Karakus et al. highlights the functional similarities between fennel PPO and tyrosinase, as both are polyphenol oxidases that catalyze the oxidation reactions of structurally similar substrates, such as catechol. Although fennel PPO is not a direct inhibitor of tyrosinase, fennel PPO demonstrates a high binding affinity for catechol, suggesting an indirect inhibition of tyrosinase through competition for the same substrates. Similarly, other nutraceuticals derived from fennel seeds, such as flavonoids and caffeic acid, may mimic natural tyrosinase substrates [18], suggesting the potential for competitive binding and decreased downstream formation of melanin precursors. These mechanisms are particularly relevant for addressing hyperpigmentation disorders like melasma, post-inflammatory hyperpigmentation (PIH), and sunspots; however, more literature is required to establish a relationship between fennel PPO and tyrosinase activity within the context of melanin synthesis.

While the inhibitory mechanisms of fennel PPO indirectly affect tyrosinase activity, existing literature highlights the synergistic effects of fennel seed extracts in modulating UV-induced melanogenesis through multi-faceted mechanisms. Specifically, a hexane fraction of *F. vulgare*, containing 13 identifiable bioactive compounds, demonstrated significant inhibition of tyrosinase, reducing enzymatic activity by 35.72%; meanwhile, trans-anethole alone showed only mild tyrosinase inhibition, reducing enzymatic activity by 10.8% [19]. This suggests that the enhanced activity of the hexane fraction is likely due to the synergistic effects of multiple constituents, including estragole, limonene, and sabinene. In addition to tyrosinase inhibition, fennel seed extracts also reduce UV-induced melanogenesis in melanoma cells through the inhibition of ORAI1 channels. These channels regulate calcium signaling in melanocytes, reducing intracellular calcium levels and subsequently melanin synthesis [19]. This dual action integrating direct tyrosinase inhibition and modulation of upstream calcium signaling highlights the broad anti-pigmentary potential of fennel seeds, making these a promising treatment for hyperpigmentation disorders, such as melasma.

Bakhtyari et al. demonstrated in a randomized, triple-blind clinical trial that a polyherbal syrup containing fennel, lemon balm, and damask rose lead to significant improvements in melasma-related outcomes compared to a placebo. Measurable indicators included reductions in melanin levels ($P = 0.017$), pigmentation intensity ($P < 0.001$), and Melasma Area and Severity Index (MASI) scores ($P < 0.001$), accompanied by an increase in skin lightness ($P < 0.001$) [20]. These findings emphasize the multifaceted biochemical mechanisms underlying fennel seed extracts, particularly their ability to neutralize oxidative stress via potent antioxidant activity. By mitigating the damaging effects of ROS and regulating cytokines such as IL-1, IL-4, and IL-6, fennel downregulates key pathways involved in melanogenesis [20]. Such effects not only validate its use as a therapeutic agent but also highlight its potential role in preventive care for skin conditions exacerbated by inflammation and oxidative stress. The anti-oxidant, anti-inflammatory, and anti-melanogenic properties of fennel extract make it a potential adjuvant modality when used alongside conventional treatments for melasma including chemical peels, hydroquinone, or laser therapy [20]. By enhancing efficacy and reducing treatment-associated complications, fennel-based combinations could bridge the gap between natural remedies and evidence-based dermatological care, catering to an increasingly health-conscious demographic seeking integrative treatment options.

In addition to its role in reducing hyperpigmentation, fennel seed extracts significantly promote fibroblast activity, reduce collagen degradation, and preserve elastin, contributing to extracellular matrix (ECM) remodeling. Fennel extract increases collagen and elastin secretion through activation of the TGF-β1 pathway, a critical regulator of fibroblast activity. Sun et al. demonstrated that fennel extract increased TGF-β1 levels by 394.5% in *in vitro* human dermal fibroblasts and 132.6% in mice after UVB-induced depletion. Fennel also promotes fibroblast resistance to oxidative stress through activation of Nrf2, an antioxidant signaling pathway critical to enabling continuous collagen synthesis [21]. Another mechanism by which fennel contributes to ECM remodeling is through downregulation of collagen-degrading enzymes, such as MMPs. Fennel extract inhibits MMPs dose-dependently through modulation of signaling molecules in the MAPK pathway, evidenced by diminished phosphorylation of ERK (68.4%) and p38 (36.8%) and decreased IL-6 levels (53.8%) [21]. Such findings position fennel as not merely a reactive agent but a proactive enhancer of dermal resilience. Bioactivity leading to enhanced collagen and elastin synthesis, resistance to oxidative stress, and reduced MMP enzymatic activity underscores fennel's role in preserving ECM integrity, which is vital for maintaining dermal health and barrier function against environmental insults, including UV-radiation.

UV- radiation damages the ECM by producing reactive oxygen species (ROS), activating MAPK signaling, and boosting MMP production, destroying collagen and elastin. Fennel counteracts these effects by activating the Nrf2 antioxidant pathway to lower oxidative stress and suppressing MAPK activation to downregulate MMPs, thus reducing collagen and elastin degradation [21]. Elastin, essential for maintaining skin elasticity, is particularly vulnerable to photodamage, making its preservation a cornerstone of anti-aging interventions. These photoprotective properties support its role in preventing UV-induced damage by reducing fine lines through increased collagen fiber and elastin density, ensuring long-term dermal health. Transcending beyond cosmetic benefits, the regulation of ECM components like collagen and elastin affect tumorigenesis due to the role of MMP-mediated ECM remodeling in tumor cell motility and invasion [21]. Fennel may impede tumor metastasis by reducing MMP activity and preserving ECM integrity, underscoring its broader therapeutic potential at the intersection of dermatology and oncology. These findings make fennel seed extract a promising natural agent for skincare formulations targeting photoaging, ECM preservation, and dermal health.

Molecular Targets in Oncology

Fennel plays a crucial role in modulating oxidative stress in skin cells and melanocytes, where its bioactive compounds act as powerful antioxidants to maintain cellular integrity. Oxidative stress in these cells can lead to DNA damage, altered signaling pathways, and an imbalance in melanin production, positioning ROS as a molecular target in cancer therapies [22]. Compounds like fennel help neutralize ROS generated by environmental stressors, including UV radiation and pollution. By reducing ROS levels, fennel prevents the peroxidation of lipids in cell membranes and the oxidation of proteins, safeguarding cellular integrity and function [23]. This activity is particularly important in melanocytes, where oxidative stress can disrupt melanin synthesis pathways, leading to pigmentation disorders [24]. Fennel-derived antioxidants also protect DNA in skin cells from oxidative damage, minimizing the risk of strand breaks, mutations, and chromosomal aberrations. This DNA protective effect is crucial in reducing UV-induced mutagenesis, a process that can trigger the early stages of skin carcinogenesis. Additionally, fennel's compounds enhance the skin's natural enzymatic antioxidant defenses, such as superoxide dismutase and catalase, further fortifying cellular resilience against oxidative stress [25]. By mitigating oxidative damage, fennel helps maintain skin tone and texture while reducing signs of photoaging, such as wrinkles and dark spots, while its protective effects against UV-induced mutagenesis reduce the risk of tumor formation, providing a natural shield against skin cancer development.

In a recent study, *Foeniculum vulgare* demonstrated significant potential in disrupting the NF-κB and MMP-9 pathways, which are critical in tumor progression and invasion [26]. NF-κB, a transcription factor linked to inflammation and oncogenesis, regulates the expression of MMP-9, an enzyme that degrades the ECM, facilitating tumor cell invasion and migration [27,28]. Fennel's bioactive compounds inhibit NF-κB activation, thereby reducing the production of pro-inflammatory cytokines and MMP-9 expression. This suppression of MMP-9 limits ECM breakdown, a process crucial for cancer cells to invade surrounding tissues and metastasize. In melanoma models, treatment with fennel essential oil resulted in decreased NF-κB and MMP-9 levels, impairing cell motility and migration [26]. Additionally, these effects were observed in both tumor cells and their stromal microenvironment [26], indicating a dual action targeting both autocrine and paracrine signaling. By reducing ECM degradation and inflammatory signaling, fennel essential oil not only restricts tumor progression but also creates a less favorable environment for cancer growth and metastasis.

Additionally, fennel demonstrates significant anticancer potential by modulating apoptotic pathways, notably through the induction of caspase-dependent apoptosis. While the precise mechanisms of this pathway in melanoma cells remain incompletely elucidated, existing studies suggest that fennel's bioactive compounds can activate caspases, a family of proteases critical for orchestrating apoptosis. This activation facilitates the systematic dismantling of cellular structures, ultimately reducing tumor cell viability [29]. Although these findings were initially reported in breast cancer cell lines, they hold relevance for melanoma, as dysregulated caspase activation is also implicated in the pathogenesis of melanoma [30]. Furthermore, the influence of NFκB extends beyond MMPs, as it also regulates the expression of genes involved in apoptosis, such as the anti-apoptotic gene Bcl2 and the pro-apoptotic gene Bax. The balance between Bcl-2 family proteins is crucial for mitochondrial-mediated apoptosis, and its dysregulation is a hallmark of cancer. *Foeniculum vulgare* influences the balance of Bcl-2 family proteins by upregulating pro-apoptotic proteins like Bax and downregulating anti-apoptotic proteins like Bcl-2, thereby promoting the release of cytochrome c from mitochondria, a pivotal step in apoptosis initiation [31,32]. This ability to selectively modulate the Bcl-2/Bax ratio highlights *Foeniculum vulgare* as a promising candidate for more effective and targeted cancer treatments. Its dual action on apoptotic pathways and tumor microenvironment remodeling suggests a multifaceted approach to impair tumor progression and metastasis, further underscoring its potential as a selective and precise anticancer agent.

Future Implications and Challenges in Fennel Seed Applications

The application of fennel seeds in dermatology and oncology is complicated by their tendency to increase photosensitivity, amplifying susceptibility to UV-induced damage. Fennel seeds contain furocoumarins such as psoralene, 5-methoxypsoralene (bergapten), and imperatorin, which are known for their phototoxic properties [33,34]. These compounds can sensitize the skin to UV radiation, making the skin more prone to damage. Psoralen, the most prevalent furocoumarin, can cause phytophotodermatitis, a non-immunologic phototoxic skin reaction when combined with UVA light [35]. This inflammatory cascade damages skin cells and disrupts normal cellular function. The skin reaction arises from psoralens cross-linking with DNA in skin cells, causing damage that manifests as skin eruptions, such as hyperpigmentations, erythema, vesicles, and bullae [35,36,37]. This process interferes with normal cellular repair and triggers oxidative stress, furthering tissue damage. The mechanism of photosensitivity involves the generation of toxic oxyradicals and a highly reactive excited state upon photon absorption, resulting in skin injury, including full-thickness burn-like wounds [37]. While fennel seeds offer therapeutic potential, their use requires caution to mitigate these phototoxic effects for safety.

The incorporation of protective measures, such as consistent sunscreen use, is essential to counteract the risk of phototoxicity. The application of broad-spectrum sunscreen is a preventive strategy against UV-induced skin damage by mitigating the harmful effects of UV radiation, which exacerbates skin reactions caused by photosensitivity-inducing chemicals in fennel seeds. Moreover, wearing protective clothing, such as long-sleeved shirts, wide-brimmed hats, and sunglasses, offers a physical barrier defense against UV radiation, reducing the risk of developing phytophotodermatitis and other skin-related manifestations resulting from phototoxicity and photosensitivity. Adjusting the formulation through special processing methods to lower the concentration of psoralen in products further helps mitigate the risk of these adverse effects [35]. These combined strategies highlight the importance of proactive measures in skin health while enabling the therapeutic potential of fennel seeds.

Another compound found in fennel seeds, estragole, has raised safety concerns due to its potential genotoxic and carcinogenic properties, particularly when consumed in high doses. Studies in rodents have demonstrated its ability to form DNA and hemoglobin adducts, which are indicative of potential carcinogenic activity [38]. While estragole has shown genotoxic

and carcinogenic properties in animal studies, its effects on humans, especially at normal dietary levels, remain a topic of debate. However, the genotoxicity of estragole appears to be significantly reduced when present in complex botanical mixtures, such as those found in fennel seed [39]. This suggests that other bioactive compounds within these mixtures may dampen the harmful effect of estragole. In addition, in vitro studies using human liver cells have shown that estragole does not induce DNA damage or apoptosis [40]. Further research is needed to clarify and understand the risk profile of estragole in humans, including long-term safety at both dietary and therapeutic doses, to fully assess the benefits and risks of fennel seeds.

There are several limitations and considerations to address for the effective use of fennel seeds. Ensuring the stability of fennel seed formation is important, as the extraction and incorporation of fennel oil into dermatological products must preserve the integrity and activity of its bioactive compounds over time, preventing degradation and maintaining a stable release profile [41]. Once applied, improving the bioavailability and skin penetration of fennel seed formations is needed to maximize the therapeutic effects. Techniques such as solid lipid nanoparticles and other advanced delivery systems, which have been successfully used with other herbal extracts, could potentially increase skin retention and controlled release of fennel seeds [42]. Continued research into the development of advanced delivery systems and formulation techniques will be key to overcoming these limitations and maximizing the therapeutic benefits of fennel seed in dermatology and oncology.

Both topical and oral applications of fennel seeds provide distinct advantages and limitations for enhanced skin targeting. Topical applications are typically more effective for localized skin treatment, while oral applications have systemic benefits that affect the skin. Topical applications are effective for the direct delivery of products to the skin, delivering higher concentrations of active compounds to the superficial layers of the skin compared to oral applications [43]. Some formations have been shown to improve the stability, penetration, and efficacy of topical treatments [44]. However, topical applications may require frequent reapplication which can pose challenges to patient adherence. Topical applications are also limited by the skin barrier, which can restrict the penetration of active ingredients if not formulated properly with an effective delivery system [44]. Oral application, on the other hand, can improve skin health by providing systemic nutrition and addressing underlying systemic factors that affect the skin [45], but they cannot directly target the skin. Each approach has unique advantages, and the choice between them should be based on the specific treatment goal and the patient's preferences. Combining both methods may offer greater efficacy in improving overall skin targeting and treatment outcomes. Further investigations are needed to better understand the optimal applications of fennel seed in both topical and oral forms.

Currently, no fennel seed-based therapies have received approval from the Food and Drug Administration (FDA) for clinical use. FDA approval requires extensive clinical trials that demonstrate not only the safety and efficacy of treatment but also its long-term outcomes and benefits. Fennel seed therapies remain a novel and under-researched area, with limited clinical evidence available to support widespread clinical use. The lack of standardized formulation and dosage guidelines is a significant challenge in obtaining FDA approval to ensure consistent quality and effectiveness. Variations in the concentration of bioactive compounds, such as furocoumarins and estragole, can affect the therapeutic outcomes and safety profiles. More comprehensive, well-designed clinical trials are needed to meet FDA standards. Additional research into optimal delivery systems, potential side effects, and interactions with other treatments is also necessary to fully understand the therapeutic effect of fennel seeds. More efforts should be made to integrate fennel seed-based products into dermatological and oncological protocols to provide natural and adjunctive therapeutic options in addition to conventional medical therapies for patients.

Additional Applications and Future Directions

Beyond its role in hyperpigmentation, aging, and tumorigenesis, emerging literature suggests fennel seeds may play a role in androgen-related dermatological conditions. Anti-hirsutism activity of fennel extract facilitates decreased hair thickness in cases of mild to moderate hirsutism. Akha et al. found that 3% fennel gel was effective in treating idiopathic hirsutism without major side effects by causing hair diameter reduction. This effect was attributed to the estrogenic activity of anethol, dieanethol, and its polymers, which inhibit 5-α-reductase and increase the conversion of testosterone to weaker androgens, thereby reducing the available testosterone stores for conversion to DHT in dermal papillae [47]. These findings suggest a broader therapeutic role for fennel extract in managing hirsutism. Large-scale randomized clinical trials are needed to elucidate the efficacy of local applications of fennel seed extracts in treating severe hirsutism and investigate any long-term side effects. A standardization protocol is also necessary to develop dosing regimens and stabilization procedures, striking a balance between efficacy and potential risks.

In addition to its anti-hirsutism properties, fennel extract's ability to modulate androgen metabolism highlights its potential applications in other androgen-dependent conditions, such as androgenic alopecia (AGA) and acne vulgaris. The role of androgen receptors has been implicated in cutaneous physiology secondary to androgenic steroidogenesis enzyme expression in the skin. AGA is caused by DHT binding to androgen receptors in hair follicles, leading to progressive hair thinning [48]. The activity of anethol against 5-α-reductase could make fennel extracts a promising candidate for managing AGA; however, further research is required to explore this relationship. Moreover, androgens stimulate sebaceous glands to produce excess sebum, contributing to acne development [48]. Fennel extract's anti-androgenic properties may reduce sebaceous gland activity, making it a potential adjunct therapy for acne. Advances in fennel seed drug formulation could explore the interplay between fennel extract and topical anti-androgens to enhance treatment outcomes for AGA and acne vulgaris.

Fennel seed extracts function as natural adjuvants to dermatological and oncological treatments through synergistic interactions with existing therapeutic agents. For instance, Kwiatkowski et al. demonstrated that combining fennel essential oil with hydrogen peroxide exhibited a synergistic effect against *Staphylococcus aureus* biofilms, which are often implicated in common skin infections. Additionally, fennel seed essential oil combination therapy with mupirocin, a topical antibiotic, provided enhanced antibacterial activity against *Staphylococcus*

aureus [50]. Despite these promising findings, clinical research is necessary to validate these synergistic effects in real-world applications. Further research can also explore the spectrum of antimicrobial activity provided by fennel seed extracts and correlate these findings with different bacterial strains and infection types. At the intersection of dermatology and oncology, fennel seed compounds can potentiate the chemotherapeutic effects of existing therapies. Prior research indicates that combination therapy including anethole and cisplatin showed increased inhibition of cancer cell proliferation compared to cisplatin alone, suggesting a potential role for fennel-derived compounds in enhancing chemotherapy efficacy [51]. Though cisplatin is rarely used in the first-line treatment of dermatologic neoplasms, future efforts should investigate fennel oil as a topical or oral adjuvant for the treatment of skin cancer due to its robust anti-carcinogenic properties. Clinical validation and expanded research on fennel's antimicrobial and anticancer mechanisms are needed to fully elucidate the synergistic potential of these compounds and translate these findings into practical applications.

Conclusion

In conclusion, the multifaceted bioactive properties of fennel seeds underscore their potential as a natural agent that can serve to bridge dermatology and oncology. Their antioxidant, anti-inflammatory, and anticancer activities, driven by compounds such as estragole, chavicol, and anethole, position them as promising therapeutic candidates. Fennel seeds not only promote skin health by mitigating oxidative stress and enhancing collagen synthesis, but also exhibit tumor-suppressive properties through the modulation of apoptotic pathways and inhibition of tumor progression mechanisms. Despite these promising findings, challenges such as phototoxicity, genotoxicity, and formulation stability must be addressed to ensure safe and effective applications. Advances in drug delivery systems and further clinical studies are needed to translate fennel seed-based therapies from experimental to clinical use. By continuing to explore their synergistic potential with existing dermatological and oncological treatments, fennel seeds offer the possibility to expand the availability of natural therapeutic options in these fields, enhancing patient care and clinical outcomes.

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