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Plant-Derived Agents Targeting Apoptotic Pathways in Non-Melanoma Skin Cancer: Mechanisms and Nanoformulation Strategies

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Abstract: Non-melanoma skin cancer (NMSC) remains the most common cutaneous malignancy and continues to rise globally, creating a growing need for safer and more effective therapeutic strategies. Dysregulation of apoptosis represents a central feature of both basal cell carcinoma and cutaneous squamous cell carcinoma, offering a rational target for intervention. Numerous plant-derived products exhibit selective pro-apoptotic activity in NMSC models, acting through mitochondrial dysfunction, caspase activation, modulation of BCL-2 family proteins, and restoration of p53-linked pathways. However, their clinical translation is limited by poor solubility, instability, and restricted skin penetration. Advances in nanoformulation technologies, including polymeric, lipid-based, and invasome systems, substantially enhance the delivery, bioavailability, and therapeutic performance of these phytochemicals. This review examines the therapeutic potential of plant-derived pro-apoptotic agents and nanodelivery systems as a forward-looking direction for next-generation NMSC management.

Keywords: non-melanoma skin cancer; apoptosis; resveratrol; curcumin; nanoformulation

1. Introduction

Non-melanoma skin cancer (NMSC) represents the most common group of cutaneous malignancies and continues to show a rising global incidence [1,2]. The scale of disease reflects both the high frequency of new diagnoses and the substantial number of patients requiring repeated interventions over time. The clinical and economic burden of NMSC therefore extends beyond mortality, influencing healthcare systems through treatment demand, follow-up requirements, and long-term surveillance needs [2,3]. Basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC) constitute the predominant forms of NMSC, while several rarer entities, including Merkel cell carcinoma (MCC) and adnexal carcinomas, contribute to the overall disease spectrum [1,4,5]. These tumours differ in biological behaviour, metastatic potential, and prognosis, creating a heterogeneous clinical landscape that requires precise diagnostic and therapeutic decision-making [4,5].

Current management of NMSC relies on surgical, topical, radiotherapeutic, targeted, and immunotherapeutic approaches, each offering specific advantages but also carrying limitations related to toxicity, accessibility, cosmetic outcomes, or treatment resistance [3,5]. Surgical excision remains the standard of care for most localized lesions, yet not all patients are suitable candidates, and recurrence remains a persistent concern [6]. Therapeutic limitations become more pronounced in advanced or high-risk disease, when aggressive tumour biology, anatomical constraints, or comorbidities may restrict the effectiveness of conventional interventions [5]. The need for alternative or adjunctive strategies is further reinforced by the rising incidence of NMSC and the increasing number of patients requiring repeated or multimodal treatment [2].

Apoptosis dysregulation represents a central biological feature in NMSC, contributing to tumour persistence, therapeutic resistance, and progression. Restoration of apoptotic signalling therefore emerges as a rational direction for therapeutic innovation, particularly in settings where conventional treatments fail to achieve adequate tumour control. Plant-derived agents, including apigenin, curcumin, resveratrol, and silymarin, have gained increasing attention as potential modulators of apoptosis in NMSC, supported by evidence of selective cytotoxicity and favourable safety profiles in preclinical models [7]. Interest in these compounds aligns with the broader need for therapeutic strategies that combine efficacy with reduced toxicity, especially in patients requiring repeated or

long-term management [3,5]. This review examines the emerging role of apoptosis-modulating phytochemicals and nanodelivery systems in next-generation therapeutic strategies for NMSC.

2. General Considerations on Non-Melanoma Skin Cancer

2.1. Epidemiology and Disease Spectrum

NMSC represents a broad category of malignant tumours arising from non-melanocytic cells of the epidermis and skin appendages, with a continuously rising global incidence [1–3]. Based on Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease estimates, the number of incident cases increased gradually from 5.73 million in 2013 to 7.17 million in 2023 (Figure 1) [8].

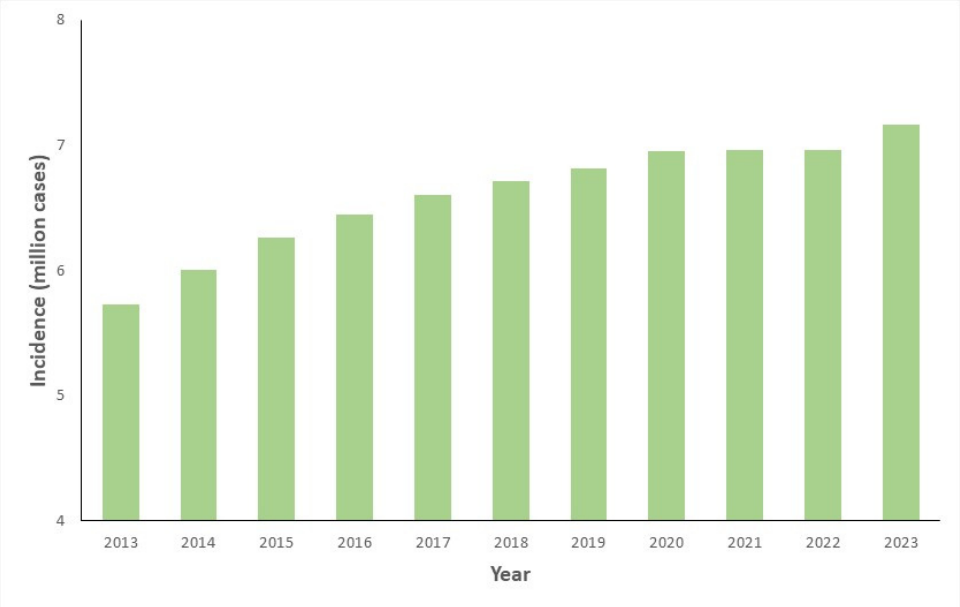

Figure 1. Global incidence of non-melanoma skin cancer over 2013–2023. The figure shows the annual estimated number of incident non-melanoma skin cancer cases worldwide, including both sexes and all ages. Data were obtained from the IHME Global Burden of Disease Results.

BCC and cSCC constitute the predominant forms and account for most NMSC cases worldwide [2,3]. Additional but less common entities, including MCC, extramammary Paget's disease, and adnexal carcinomas such as apocrine adenocarcinoma and sebaceous carcinoma, contribute to the clinical diversity of NMSC [4]. Precise histopathological diagnosis remains essential for selecting appropriate therapeutic strategies [1]. BCC originates from basal keratinocytes in the deepest epidermal layer or the outer root sheath of hair follicles and represents 70–80% of NMSC cases, typically showing slow growth and minimal metastatic potential [5,9]. cSCC arises from more differentiated keratinocytes in the upper epidermis, accounts for 20–25% of NMSC cases and displays more aggressive behaviour with higher risks of metastasis and disease-specific mortality [9]. MCC, although rare, develops from Merkel neuroendocrine cells and is characterized by rapid progression, high recurrence rates, and poor prognosis [5].

2.2. Global Burden and Epidemiological Trends

The global burden of NMSC has increased substantially over recent decades. NMSC accounts for 99% of all skin cancer cases and contributes significantly to healthcare costs and morbidity despite relatively low mortality [2,4,10]. In 2021, NMSC caused tens of thousands of deaths and more than one million disability-adjusted life years (DALYs), reflecting its major public health impact [2]. Incidence continues to rise across all regions, particularly in high socio-demographic index countries, where increased UV exposure, aging populations, and improved diagnostic practices contribute to higher detection rates. Reported increases in BCC and cSCC incidence exceed 290% and 320%, respectively, since 1990 [10].

2.3. Etiology, Risk Factors, and Molecular Drivers

Ultraviolet (UV) radiation represents the primary etiological driver of NMSC. Chronic UV exposure induces deoxyribonucleic acid (DNA) damage through cyclobutane pyrimidine dimers and other photoproducts, leading to characteristic mutations in tumour suppressor genes such as the gene encoding tumour protein 53 (*TP53*) and dysregulation of pathways controlling proliferation and apoptosis. Approximately 90% of NMSC cases are attributed to UV radiation, which also promotes oxidative stress, local immunosuppression, and chronic inflammation [11]. Additional risk factors include advanced age, male sex, immunosuppression, viral infections such as human papillomavirus (HPV), smoking, and chronic inflammatory conditions [10,12]. Genetic predisposition further influences susceptibility; disorders affecting DNA repair, such as Xeroderma pigmentosum, confer extreme UV sensitivity and markedly increased cancer risk [6]. At the molecular level, BCC is driven predominantly by aberrant activation of the Hedgehog signalling pathway, whereas cSCC is associated with *TP53* mutations and dysregulation of the epidermal growth factor receptor (EGFR) pathway [11].

2.4. Current Therapeutic Landscape

The therapeutic landscape of NMSC includes surgical, intralesional, topical, radiotherapeutic, targeted, and immunotherapeutic approaches [5,7]. Surgical excision remains the gold standard for localized disease, offering high cure rates and favourable outcomes [6]. Mohs micrographic surgery provides superior margin control and tissue preservation, particularly in high-risk or cosmetically sensitive areas [13]. Topical 5-fluorouracil (5-FU) is used for low-risk superficial BCC and acts by disrupting nucleotide synthesis and incorporating abnormal uracil analogues into DNA and ribonucleic acid (RNA), leading to selective destruction of atypical keratinocytes [3]. Cure rates of approximately 80% at one year are reported, although erythema and local infection occur more frequently than with imiquimod [3,7]. Intralesional methotrexate and 5-FU have been explored in cSCC, but limited tissue penetration restricts their effectiveness in larger or high-risk tumours [6]. Imiquimod, a topical immunomodulator acting through Toll-like receptor 7 (TLR7), is approved for superficial BCC and achieves response rates of around 83% at one year, though its role in nodular BCC remains limited and treatment often causes local irritation, ulceration, and pain [3].

Cryosurgery is effective for small, low-risk superficial BCCs but is generally avoided in cSCC due to higher metastatic risk. Recurrence rates may reach 20%, and side effects include edema, neuropathic pain, scarring, hypopigmentation, alopecia, and other pigmentary changes [3,7]. Electrodesiccation and curettage are cost-effective options for low-risk BCC but show reduced effectiveness in high-risk tumours [3,6]. Radiotherapy is used when surgery is not feasible or as adjuvant therapy, particularly for large tumours on the head or face [5,6]. It is contraindicated in inherited cancer-predisposition syndromes such as basal cell nevus syndrome, Xeroderma pigmentosum, and Li-Fraumeni syndrome. Photodynamic therapy offers a non-invasive option for superficial BCC, Bowen's disease, and actinic keratoses, providing good tolerability and excellent cosmetic outcomes, though its effectiveness is limited in aggressive BCC subtypes and invasive cSCC [3,7]. Laser therapies have been explored, with better outcomes in in situ lesions than in invasive cSCC [7].

Systemic therapies play a central role in advanced disease. Hedgehog pathway inhibitors (HHIs), including vismodegib and sonidegib, are effective in locally advanced or metastatic BCC but are limited by adverse effects and treatment resistance [3,6]. Immunotherapy with programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors (pembrolizumab, cemiplimab, avelumab) or cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) inhibitors (ipilimumab) has become increasingly important for advanced cSCC and HHI-refractory BCC [7]. Cemiplimab has demonstrated meaningful clinical efficacy but requires careful monitoring for immune-related adverse events [3]. EGFR-targeted therapies such as cetuximab and panitumumab are used in advanced or unresectable cSCC, achieving disease control rates of about 69% at six weeks, though adverse effects are common [6].

Only one plant-derived agent, namely ingenol mebutate, a diterpene ester isolated from *Euphorbia peplus*, has advanced to clinical trials for the treatment of NMSC. In 2013, ingenol mebutate gel (Picato®) was authorized by the European Medicines Agency (EMA) for the topical treatment of actinic keratosis, a skin lesion that may progress to SCC [7]. Ingenol mebutate has been shown to induce rapid cell death in dysplastic keratinocytes and to activate protein kinase C (PKC)-dependent inflammatory responses, contributing to lesion clearance [14]. Safety studies identified a higher incidence of SCC in patients using the gel and, therefore, seven years later, the EMA recommended the suspension of its marketing authorization [7].

Despite therapeutic advances, adverse effects and recurrence remain major concerns, highlighting the need for more effective preventive strategies and novel therapeutic agents with improved safety profiles [2].

3. Apoptosis as a Target in Non-Melanoma Skin Cancer

3.1. Biological Role of Apoptosis in Skin Homeostasis and Cancer

Apoptosis represents a tightly regulated form of programmed cell death characterized by distinct morphological and biochemical features, including DNA fragmentation, chromatin condensation, cell shrinkage, and membrane blebbing [15]. Normal skin homeostasis relies on apoptosis to eliminate damaged or mutated keratinocytes, thereby preventing malignant transformation [16,17]. In cancer, apoptotic pathways are frequently disrupted, resulting in reduced cell death and enhanced survival of malignant cells, which support tumour growth and disease progression [17]. In NMSC, particularly BCC and cSCC, dysregulation of apoptotic signalling constitutes a central mechanism underlying tumour development and persistence. BCC commonly exhibits elevated expression of anti-apoptotic proteins such as B-cell lymphoma 2 (BCL-2), whereas cSCC frequently displays *TP53* mutations and defects in death receptor signalling. These alterations collectively enable malignant keratinocytes to evade programmed cell death, establishing apoptosis as a key therapeutic target in NMSC [18].

3.2. Core Apoptotic Pathways

Apoptosis proceeds through two major signalling routes: the intrinsic (mitochondrial) pathway and the extrinsic (death receptor) pathway. Although initiated by different stimuli, both converge on the activation of effector caspases through a sequential proteolytic cascade that drives the characteristic morphological and biochemical features of apoptosis (Figure 2) [15].

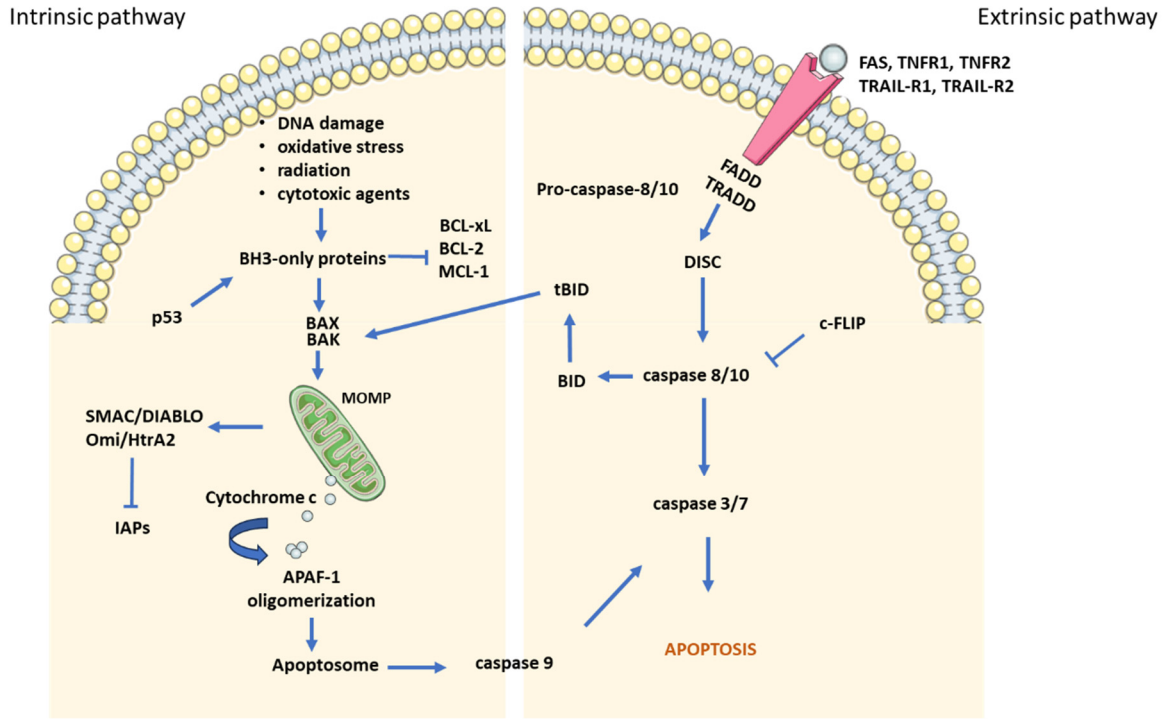

Figure 2. Intrinsic and extrinsic pathways of apoptosis.

APAF-1, apoptotic protease activating factor 1; BAK, BCL-2 homologous antagonist/killer; BAX, BCL-2-associated X protein; BCL-2, B-cell lymphoma 2; BCL-xL, BCL-extra-large; BH3, BCL-2 homology 3; BID, BH3 interacting-domain death agonist; c-FLIP, cellular FLICE-inhibitory protein; DISC, death-inducing signalling complex; FADD, FAS-associated death domain protein; IAPs, inhibitor of apoptosis proteins; MCL-1, myeloid cell leukemia 1; MOMP, mitochondrial outer membrane permeabilization; Omi/HtrA2, high temperature requirement protein A2/Omi stress-regulated endoprotease; SMAC/DIABLO, second mitochondria-derived activator of caspases/direct IAP-binding protein with low pI; tBID, truncated BID; TNFR1/2, tumour necrosis factor receptor 1/2; TRADD, TNF receptor type 1-associated death domain protein; TRAIL-R1/2, TNF-related apoptosis-inducing ligand receptor 1/2.

3.3. Intrinsic (Mitochondrial) Apoptotic Pathway

The intrinsic pathway is activated by intracellular stressors such as DNA damage, oxidative stress, radiation, or cytotoxic agents [19]. These signals engage BH3-only proteins of the BCL-2 family, which function as sensors of cellular injury and shift the balance toward apoptosis [20,21]. BH3-only proteins promote apoptosis either by directly activating the pro-apoptotic effectors BCL-2-associated X protein (BAX) and BCL-2 homologous antagonist/killer (BAK) or by inhibiting anti-apoptotic members such as BCL-2, BCL-extra-large (BCL-xL), and myeloid cell leukemia 1 (MCL-1) [19,21]. Activated BAX and BAK oligomerize within the mitochondrial outer membrane, inducing mitochondrial outer membrane permeabilization (MOMP), a decisive and irreversible step in intrinsic apoptosis [19–21].

MOMP enables the release of apoptogenic factors, including cytochrome c, which binds apoptotic protease activating factor-1 (APAF-1) to form the apoptosome in the presence of adenosine triphosphate (ATP). This complex activates caspase-9 and subsequently the effector caspases-3 and -7 [20]. Additional mitochondrial proteins, including SMAC/DIABLO and Omi/HtrA2, enhance apoptosis by inhibiting inhibitor of apoptosis proteins (IAPs), while apoptosis-inducing factor (AIF) contributes to caspase-independent DNA fragmentation [19–21]. The pathway is further regulated by anti-apoptotic BCL-2 proteins that preserve mitochondrial integrity and by p53, which promotes apoptosis through transcriptional activation of BH3-only proteins such as PUMA and NOXA [19,21].

3.4. Intrinsic Pathway Dysregulation in NMSC

Intrinsic apoptotic signalling is frequently impaired in NMSC. BCC typically shows elevated expression of anti-apoptotic BCL-2 family members, which stabilize mitochondrial membranes and enhance resistance to apoptosis [22]. In cSCC, *TP53* mutations compromise the transcriptional activation of BH3-only proteins such as PUMA and NOXA, reducing mitochondrial readiness for apoptosis. These alterations collectively diminish intrinsic apoptotic responses and support malignant keratinocyte survival [23].

3.5. Extrinsic (Death Receptor) Apoptotic Pathway

The extrinsic pathway is initiated by the binding of extracellular death ligands to specific cell-surface receptors, including FAS cell surface death receptor (FAS/CD95), tumour necrosis factor receptor 1 (TNFR1), tumour necrosis factor receptor 2 (TNFR2), and the tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors DR4/TRAIL-R1 and DR5/TRAIL-R2 [19–21]. Ligand binding induces receptor trimerization and exposure of intracellular death domains, which recruit adaptor proteins such as FAS-associated death domain (FADD) and, in the case of TNFR1, TRADD [19,20]. These interactions promote assembly of the death-inducing signalling complex (DISC), where procaspase-8 and procaspase-10 are activated through dimerization, a process inhibited by cellular FLICE-inhibitory protein (c-FLIP) [19,21]. Activated caspase-8 initiates apoptosis either by directly activating effector caspases-3 and -7 or by cleaving BH3-interacting domain death agonist (BID) into truncated BID (tBID), which translocates to mitochondria and promotes BAX/BAK-mediated permeabilization, thereby linking the extrinsic and intrinsic pathways [20,21].

3.6. Extrinsic Pathway Dysregulation in NMSC

Alterations in extrinsic apoptotic signalling contribute significantly to apoptosis resistance in NMSC. In cSCC, reduced expression or impaired function of FAS and TRAIL receptors, together with elevated c-FLIP levels, interferes with DISC formation and inhibits caspase-8 activation [23,24]. These defects weaken immune-mediated apoptosis and promote tumour persistence [23]. Overexpression of IAPs, including survivin, further suppresses downstream caspase activity and reinforces apoptosis resistance [25].

3.7. Therapeutic Relevance of Apoptotic Dysregulation

Apoptotic signalling is disrupted at multiple regulatory levels in NMSC. In BCC, overexpression of BCL-2 stabilizes mitochondrial membranes and prevents cytochrome c release, while reduced BAX activity further limits intrinsic apoptotic initiation [22]. Persistent Hedgehog pathway activation promotes anti-apoptotic signalling and suppresses p53-dependent pro-apoptotic mediators. In cSCC, *TP53* mutations impair intrinsic pathway activation, and defects in death receptor signalling reduce responsiveness to extrinsic apoptotic cues [24]. Elevated c-FLIP and IAP expression further inhibits caspase activation and promotes survival [25]. These alterations collectively support tumour growth, therapeutic resistance, and recurrence, while identifying BCL-2 family proteins, p53, death receptors, c-FLIP, and IAPs as promising therapeutic targets in NMSC [26].

4. Plant-Derived Products Triggering Apoptosis in Non-Melanoma Skin Cancer

4.1. Rationale for Apoptosis-Based Phytotherapy in NMSC

Inducing apoptosis in tumour cells represents a central anticancer strategy because it limits inflammation and preserves tissue integrity. Tumour cells frequently evade apoptotic signalling through *TP53* mutations, overexpression of anti-apoptotic proteins such as BCL-2 and IAPs, activation of pro-survival pathways including phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), loss or impairment of BAX and BAK, and direct caspase inactivation [19,27]. Agents that trigger apoptosis preferentially target malignant cells with dysregulated apoptotic machinery, while sparing normal cells with intact pathways, thereby exhibiting selective cytotoxicity [28]. These agents also avoid pro-inflammatory and tissue-damaging effects associated with necrotic cell death [19].

Plant-derived extracts and purified phytochemicals have gained substantial interest due to their ability to activate intrinsic and extrinsic apoptotic pathways in cancer cells. Their activity often involves increased reactive oxygen species (ROS) production, mitochondrial membrane depolarization, cytochrome c release, and activation of caspase-9 and caspase-3, together with modulation of BAX, BCL-2, BCL-XL, survivin, and other regulators of cell survival [29]. This section summarizes plant extracts (Table 1) and secondary metabolites (Table 2, Figure 3) that induce apoptosis in NMSC and represent promising candidates for safer and more selective anticancer therapy.

Table 1. Plant extracts triggering apoptosis in non-melanoma skin cancer.

Plant Species	Plant Material	Extraction Type	Concentration	Cell Line	Molecular Mechanism	Ref.
Curcuma longa L.	rhizome	dichloromethane extract	20 µg/mL	A431	↑ DNA fragmentation, BAX, p53	[30]
Vanilla planifolia Jacks. ex Andrews	leaves	ethanolic extract	IC_{50} = 31.2 µg/mL	A431	↑ DNA damage/DNA fragmentation	[31]
Wrightia tinctoria (Roxb.) R.Br.	leaves	ethanolic extract	IC_{50} = 78.44 µg/mL	A431	↑ DNA laddering/ internucleosomal DNA cleavage, casp-3	[32]

BAX = BCL-2-associated X protein; casp—caspase.

Table 2. Phytochemicals triggering apoptosis in non-melanoma skin cancer.

Class of Compounds	Compounds	Concentration	Cell Line	Molecular Mechanism	Ref.
Alkaloids	Cryptolepine	2.5 µM; 5.0 µM; 7.5 µM for 24 h	SCC-13, A431	↑ DNA damage, p53, p16, p21, BAX, BCL-2, cytochrome c release ↓ MDM2, ΔΨm	[33]
	Sanguinarine	0.5–16 µM for 24 h	A431, A388	↑ sub-G0/G1 apoptotic fraction, intracellular /mitochondrial ROS, JNK phosphorylation/activation, BAX, casp-3, -8, -9, PARP cleavage, MAPK, p38, ERK1/2 ↓ ΔΨm, BID	[16]
Flavonoids	Apigenin	40–80 µM for 6–48 h	JB6 (TPA-induced epidermal cells), A431	↑ casp-3, -8, PARP, p-p38, p-ERK, p-JNK, BAX ↓ SRX, Nrf2, BCL-2	[34]
	(+)-Cyanidan-3-ol	25–100 µM for 24–72 h	A431	G2/M cell cycle arrest ↑ cytochrome c release, ATM, Chk2, CDC25C, p21, casp-3, casp-3/7, PARP, ATF3, BAX, JNK ↓ CIP2A, cyclin B1, CDK1, AKT phosphorylation, survivin, cyclin D1, CDK4, BCL-xL	[35]
	Licochalcone B	5–20 µM for 24–48 h	A431	↑ nuclear condensation, membrane blebbing, cell shrinkage, DNA fragmentation, PARP, BAX, APAF-1, p21, p27, CHOP, DR4, DR5 ↓ Sp1, MCL-1, survivin, ΔΨm, BCL-2, BID	[15]
	Silymarin/ Silibinin	100–200 µM	JB6 P+, A431	↑ p53, p-Ser15, p21, p27, casp-3, PARP ↓ BCL-2	[36]
Polyphenols	Curcumin	20–30 µM for 24 h	A431	↑ DNA fragmentation, BAX, ↓ p53, p-Ser15	[30]
	Resveratrol	IC_{50} = 57.5 mg/L	A431	↑ p53, MAPK/ERK, p38, casp-3, BAX, PARP ↓ survivin	[17]

ΔΨm, mitochondrial membrane potential; AKT, protein kinase B; APAF-1, apoptotic protease activating factor 1; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related; BAX, BCL-2-associated X protein; BID, BH3 interacting-domain death agonist; casp, caspase; CDK1, cyclin-dependent kinase 1; Chk1/Chk2, checkpoint kinases 1 and 2; CHOP, C/EBP homologous protein; DR4/DR5, death receptors 4 and 5; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MCL-1, myeloid cell leukemia 1; MDM2, murine double minute 2; Nrf2, nuclear factor erythroid 2-related factor 2; PARP, poly(ADP-ribose) polymerase; ROS, reactive oxygen species; Sp1, specificity protein 1; SRX, sulfiredoxin.

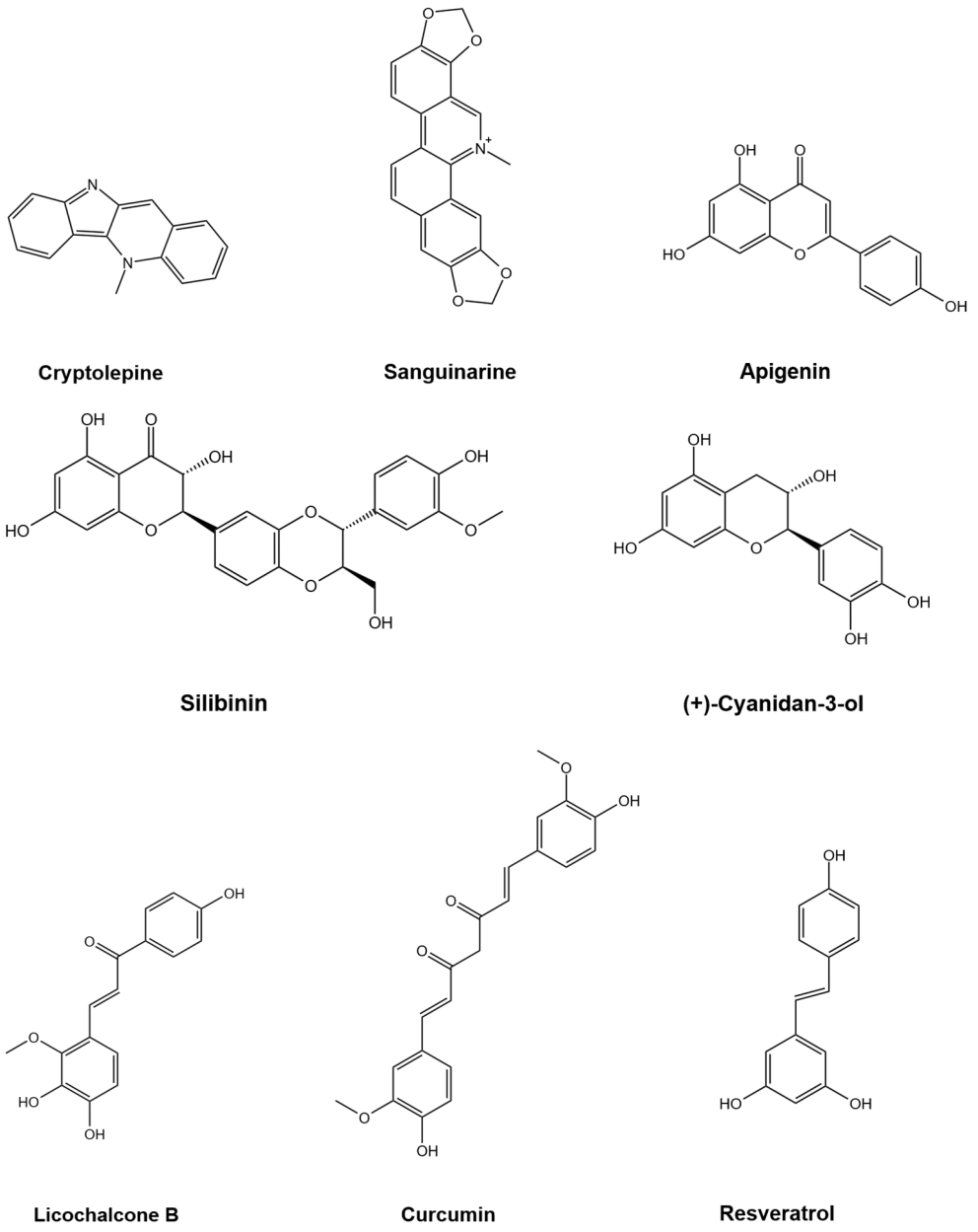

Figure 3. Phytochemicals with pro-apoptotic effects in non-melanoma skin cancer.

4.2. Curcuma longa (Turmeric)

Curcuma longa (Zingiberaceae) contains curcuminoids and numerous volatile and non-curcuminoid compounds with diverse pharmacological activities [37]. Turmeric extract induced apoptosis in A431 human skin squamous carcinoma cells, with 20 μg/mL treatment for 24 h producing a marked increase in the sub-G1 population (~30%), consistent with DNA fragmentation and apoptotic body formation. The apoptotic response involved mitochondrial signalling and BAX activation, indicating intrinsic pathway engagement. Importantly, apoptosis occurred in cells carrying mutant p53, suggesting that turmeric can bypass p53-dependent resistance mechanisms [30].

4.3. Vanilla planifolia

Vanilla planifolia (Orchidaceae) is traditionally valued for its aromatic pods and medicinal uses [38]. Ethanolic leaf extract of *V. planifolia* exhibited strong antitumour activity against A431 cells (IC50 = 31.2 μg/mL). DNA fragmentation analysis revealed clear apoptotic DNA damage and fragmentation, confirming activation of apoptotic cell death in treated cells [31].

4.4. Wrightia tinctoria

Wrightia tinctoria (Apocynaceae) contains diverse bioactive compounds with documented pharmacological activities [39]. Ethanolic leaf extract of *W. tinctoria* demonstrated potent antitumour effects against A431 cells (IC50 = 78.44 μg/mL). Treated cells exhibited hallmark apoptotic features, including shrinkage, membrane blebbing, rounding, detachment, and apoptotic body formation, particularly at higher concentrations. Acridine orange/ethidium bromide staining confirmed chromatin condensation, nuclear fragmentation, and membrane integrity loss. Flow cytometry revealed 14.6% early and 71.5% late apoptotic cells, with minimal necrosis. DNA fragmentation assays and detection of cleaved caspase-3 further supported activation of apoptotic pathways. These findings indicate that *W. tinctoria* suppresses tumour cell proliferation primarily through apoptosis [32].

4.5. Apigenin

Apigenin induced apoptosis in A431 and 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-stimulated JB6 cells through coordinated activation of extrinsic and intrinsic pathways, evidenced by increased cleaved caspase-3, caspase-8, and poly(ADP-ribose) polymerase (PARP) [34]. Mitochondrial involvement was supported by BAX upregulation and BCL-2 suppression [40]. Apigenin modulated mitogen-activated protein kinase (MAPK) signalling, increasing phosphorylation of p38 and extracellular signal-regulated kinase (ERK) and transiently activating c-Jun N-terminal kinase (JNK). Mitogen-activated protein kinase kinase 1/2 (MEK1/2) inhibition attenuated apoptosis and restored BCL-2, highlighting ERK-dependent regulation. Apigenin also suppressed antioxidant proteins sulfiredoxin (SRX) and nuclear factor erythroid 2-related factor 2 (Nrf2), weakening redox defenses and sensitizing cells to apoptosis [34].

4.6. Cryptolepine

Cryptolepine induced potent apoptosis in SCC-13 and A431 cells through activation of the p53 pathway [33]. DNA damage triggered phosphorylation and acetylation of p53, downregulation of murine double minute 2 (MDM2), and accumulation of active p53, accompanied by increased expression of downstream targets such as p16 and p21 [41]. Mitochondrial involvement was confirmed by increased BAX/BCL-2 ratio, cytochrome c release, and loss of mitochondrial membrane potential (ΔΨm) [42]. Selectivity for malignant cells was demonstrated by minimal effects on normal human epidermal keratinocytes [33].

4.7. Curcumin

Curcumin induced apoptosis in A431 cells, with 20–30 μM treatment for 24 h increasing the sub-G1 population to ~30%, consistent with DNA fragmentation. z-VAD-FMK, a pan-caspase inhibitor, abolished the sub-G1 population and partially restored viability, confirming caspase dependence. Curcumin reduced p53 levels, indicating a p53-independent apoptotic mechanism in this model [37].

4.8. (+)-Cyanidan-3-ol

(+)-Cyanidan-3-ol induced apoptosis in A431 cells through G2/M arrest, mitochondrial dysfunction, and caspase activation [35]. Treatment increased G2/M accumulation (19.0% → 38.4%), downregulated cyclin B1 and cyclin-dependent kinase 1 (CDK1), and activated ataxia telangiectasia mutated (ATM), checkpoint kinase 2 (Chk2), cell division cycle 25C (CDC25C), and p21. Apoptosis was confirmed by nuclear condensation, apoptotic body formation, cytochrome c release, DNA fragmentation, and caspase-3 activation [43]. z-VAD-FMK restored viability, confirming caspase dependence. (+)-Cyanidan-3-ol downregulated survivin, cyclin D1, CDK4, and BCL-xL, while upregulating activating transcription factor 3 (ATF3) and BAX. c-JNK activation appeared to contribute to the induction of mitochondrial apoptosis [44].

4.9. Licochalcone B

Licochalcone B induced apoptosis in A431 cells (5–20 μM, 48 h), producing membrane blebbing, shrinkage, nuclear condensation, and apoptotic body formation [15]. Sub-G1 accumulation (0.50% → 22.10%) and annexin V positivity confirmed apoptosis. Mechanistically, licochalcone B activated caspase-dependent apoptosis, increased BAX and APAF-1, decreased BCL-2 and BID, and promoted mitochondrial dysfunction [45]. It also induced G1 arrest via p21 and p27 upregulation and suppressed survival proteins, including MCL-1 and survivin. Downregulation of specificity protein 1 (Sp1) contributed to apoptotic initiation. Endoplasmic reticulum stress

induction and C/EBP homologous protein (CHOP) upregulation increased DR4 and DR5 expression, indicating crosstalk between intrinsic and extrinsic pathways [15].

4.10. Resveratrol

Resveratrol primarily induces apoptosis in NMSC through p53 activation and caspase-dependent pathways [17]. In A431 cells, resveratrol reduced viability (IC50 = 57.5 mg/L) and increased apoptosis (~39.6%). Combined treatment with 5-aminolevulinic acid photodynamic therapy (ALA-PDT) further enhanced apoptosis (~63.6%), demonstrating synergistic activity [46]. Mechanistically, resveratrol activated MAPK pathways, particularly ERK and p38, and increased expression of p53 and caspase-3 [17]. Inhibition of p38 using SB203580 attenuated both antiproliferative and pro-apoptotic effects, confirming the central role of MAPK/p38 signalling [17,46].

4.11. Sanguinarine

Sanguinarine induced apoptosis in A431 and A388 cSCC cells, with 2 μM treatment (6–48 h) reducing viability and producing caspase-3 and caspase-8 activation, DNA fragmentation, and sub-G0/G1 accumulation [16]. Mechanistically, sanguinarine activated both extrinsic and intrinsic pathways, with caspase-8 activation followed by caspase-3 cleavage and PARP degradation [47]. ROS generation, mitochondrial depolarization, BAX upregulation, and BID cleavage (tBID formation) linked the two pathways. Caspase-9 activation confirmed mitochondrial involvement. Sanguinarine also activated MAPK signalling (JNK, p38, ERK1/2), with JNK playing a central pro-apoptotic role [48].

4.12. Silibinin

Silibinin induced apoptosis in JB6 and SKH-1 epidermal models through modulation of p53 signalling, mitochondrial pathways, and pro-survival networks [36]. UVB-induced DNA damage enhanced p53 activation, including Ser15 phosphorylation, leading to increased transcription of p21 and p27 and promoting cell-cycle arrest and apoptosis [49,50].

5. Nanoformulation of Phytochemicals with Pro-Apoptotic Activity Against Non-Melanoma Skin Cancer

5.1. Barriers to Effective Cutaneous Delivery of Phytochemicals

Plant-derived products exhibit significant pro-apoptotic activity in NMSC, yet their therapeutic potential is limited by poor skin bioavailability. The stratum corneum, composed of keratin-enriched corneocytes embedded in a lipid matrix, forms a highly restrictive barrier that limits penetration of phytochemicals into epidermal keratinocytes. NMSC lesions, characterized by keratinized papules, erythematous plaques, and elevated keratin and lipid content, further impede penetration compared with normal skin. Unfavorable physicochemical properties, including low hydrophilicity or excessive lipophilicity, chemical instability, metabolism, and systemic distribution, also reduce local concentrations at the site of action [51–53]. Highly water-soluble compounds fail to cross the lipid-rich stratum corneum, whereas highly lipophilic compounds become retained within it. Although cutaneous metabolism is lower than hepatic metabolism, phytochemicals may undergo phase I–III biotransformation in the epidermis, sebaceous glands, and follicular sheath, reducing their active fraction. These limitations justify the use of nanoformulation strategies to enhance therapeutic delivery [53].

5.2. Advantages of Nanocarrier-Based Delivery Systems

Nanocarrier encapsulation improves solubility, stability, and cutaneous penetration of phytochemicals while enabling sustained and targeted release [53]. Lipid-based nanoparticles, inorganic nanoparticles, and polymer-based nanoparticles have demonstrated enhanced antitumour efficacy in skin cancer models. These systems increase drug residence time in the epidermis, facilitate penetration through the stratum corneum, and protect phytochemicals from premature degradation [54]. Each group is heterogenous and comprises various nanoformulations, whose main advantages and limitations are summarized in Table 3.

For improved antitumour efficacy, curcumin and resveratrol, phytochemicals with pro-apoptotic activity in NMSC, have been incorporated into nanodelivery systems and investigated in experimental skin cancer models.

Table 3. Nanodelivery systems in experimental skin cancer models.

Lipid-Based Nanoparticles	Ref.	Inorganic Nanoparticles	Ref.	Polymer-Based Nanoparticles	Ref.
1. Liposomes	[54,55]	**1. Functionalized metal nanoparticles**	[54,56]	**1. Functionalized polymeric nanoparticles**	[54,57]
advantages: - improved topical deposition at the action site - depot-like release on skin surface - receptor-specific targeting		**advantages:** - enhanced accumulation in cancer cells due to efficient cellular penetration - increased cytotoxicity - synergistic anticancer effects with chemotherapeutics - induction of apoptosis via ROS generation - high surface area enabling efficient functionalization and targeting		**advantages:** - enhanced cellular penetration - enhanced drug stability - prolonged drug circulation time - improved pharmacokinetics of lipophilic drugs - compatibility with immunotherapy approaches - low toxicity to healthy cells (selective action)	
limitations: - rapid reticuloendothelial system uptake and macrophage degradation - poor stratum corneum penetration - upper-skin-layer accumulation - variable entrapment efficiency - instability and drug leakage		**limitations:** - ROS-related toxicity - potential metal accumulation and systemic toxicity - limited long-term toxicity data - variability in nanoparticle performance depending on design		**limitations:** - potential immunogenicity and polymer-related toxicity - pharmacokinetic variability dependent on surface functionalization properties - manufacturing and scalability challenges - limited long-term safety data	
2. Ethosomes	[54,55,58]	**2. Carbon nanotubes**	[54,59]	**2. Dendrimers**	[54,60]
advantages: - ethanol-driven deep skin penetration - increased stratum corneum permeability - high vesicle elasticity /deformability - improved drug retention in deep skin layers - improved accumulation of bioactive compounds in skin cancer cells		**advantages:** - efficient cellular penetration and intracellular delivery - enhanced accumulation in tumour cells - increased chemical stability of chemotherapeutics - targeted delivery to cancer cells - high surface functionalization capacity		**advantages:** - high drug-loading capacity - enhanced solubility of hydrophobic drugs - targeted delivery via ligand-mediated interactions - selective accumulation in tumour tissue - capability for combined chemo- and immunotherapy - reduced off-target effects - sustained and controlled drug release - structural uniformity and low polydispersity	
limitations: - ethanol-related skin tolerability concerns - need for extensive clinical safety/efficacy validation		**limitations:** - potential cytotoxicity and pro-inflammatory effects - complex biodistribution and clearance mechanisms - size-dependent tumour penetration limitations - challenges in purification and large-scale production - possible interference with cellular structures and function		**limitations:** - biocompatibility and toxicity concerns - need for surface modification to reduce toxicity - potential cytotoxicity, especially for cationic high-generation dendrimers - hematological toxicity - membrane disruption due to electrostatic interactions - potential immunogenicity depending on surface chemistry - need for surface modification to improve biocompatibility	

Table 3. *Cont.*

Lipid-Based Nanoparticles	Ref.	Inorganic Nanoparticles	Ref.	Polymer-Based Nanoparticles	Ref.
3. Niosomes		**3. Nanofibers**			
advantages: - enhanced skin penetration - high biocompatibility - non-immunogenic and biodegradable properties - easy surface modification due to functional groups - enhanced absorption across cell membranes	[54,61,62]	**advantages:** - sustained and controlled local drug release - reduced burst release compared to nanoparticles - localized drug delivery at tumour site - reduced systemic toxicity to normal cells - decreased risk of tumour recurrence after surgery - direct application to tumour tissue avoiding systemic loss - high reproducibility and controlled morphology	[54,63]		
limitations: - physical instability during dispersion (aggregation, fusion) - risk of drug leakage during storage - potential toxicity due to surfactant segregation - risk of toxicity related to drug concentration at target site		**limitations:** - limited suitability for systemic drug delivery - potential limitations in treating metastatic disease			
4. Solid lipid nanoparticles					
advantages: - enhanced delivery of poorly soluble anticancer drugs - increased drug retention in skin and tumour tissues - high biocompatibility and low irritation - strong adhesion to skin surface - enhanced penetration across stratum corneum - high physical stability and long storage time	[54,64,65]				
limitations: - limited drug loading capacity (due to solid lipid matrix) - risk of drug expulsion during storage (polymorphic transitions) - potential particle growth and gelation over time					

5.3. Polymeric Nanoformulations of Curcumin

Poly(lactic-co-glycolic acid) (PLGA) nanopatterned films have attracted attention due to their favorable interactions with cells and their ability to modulate cellular processes, including apoptosis. PLGA nanopatterned films stabilized with tocopherol poly(ethylene glycol) 1000 succinate (TPGS) and loaded with curcumin exhibited higher cytotoxicity toward A431 cells than non-patterned films. Apoptosis represented the primary mechanism of cytotoxicity, supported by sub-G1 cell-cycle arrest and loss of mitochondrial membrane potential, with necrosis contributing to a lesser extent. *In vivo*, PLGA nanopatterned films loaded with curcumin inhibited DMBA/croton oil-induced skin carcinogenesis in Swiss albino mice, reducing epidermal hyperplasia and dermal inflammatory infiltrates [66].

Curcumin nanoparticles (2–40 nm), produced using solvent-displacement/wet-milling, showed markedly improved aqueous solubility (up to 3 mg/mL) compared with free curcumin. In A431 cells, nanocurcumin demonstrated superior antiproliferative activity at lower concentrations (10–20 mM) after 24 h, while maintaining comparable effects at 25 mM. These findings indicate enhanced cellular uptake, improved bioavailability, and increased anticancer efficacy relative to free curcumin [67].

5.4. Lipid-Based Nanoformulations of Resveratrol and Quercetin

Invasomes, unlike liposomes and ethosomes, incorporate terpenes and ethanol as penetration enhancers, enabling superior permeation across the stratum corneum. Resveratrol-loaded invasomes containing thymol exhibited an IC50 of 6.34 μg/mL against squamous carcinoma cells, demonstrating greater activity than free resveratrol and unloaded invasomes [68]. A nanostructured lipid carrier gel co-loaded with resveratrol (7.80%) and quercetin (9.20%) showed enhanced cytotoxicity and antimigratory activity in A431 cells compared with a conventional gel (IC50 = 86.50 vs. 123.64 μM; wound healing = 12.56% vs. 20.52%). Enhanced permeation and higher accumulation of both phytochemicals in skin layers were confirmed using artificial membranes and excised animal skin, supporting improved topical delivery and therapeutic potential [69].

6. Future Directions

Future progress in the management of non-melanoma skin cancer (NMSC) requires integrated strategies that combine mechanistic understanding of apoptosis with advances in phytochemical delivery. Current evidence demonstrates that plant-derived compounds activate intrinsic and extrinsic apoptotic pathways in NMSC models, yet their translation into clinical practice remains limited by poor cutaneous penetration, instability, and variable bioavailability [29,30,33]. Overcoming these delivery barriers represents a central priority for next-generation therapeutic development [51–53]. Advances in nanoformulation technologies provide a strong foundation for improving the therapeutic performance of pro-apoptotic phytochemicals. Lipid-based nanoparticles, polymeric carriers, invasomes, and nanostructured lipid systems have demonstrated enhanced solubility, stability, and epidermal penetration for compounds such as curcumin, resveratrol, and quercetin [53–58]. Optimization of particle size, surface charge, and ligand functionalization may further improve selective accumulation within NMSC lesions while minimizing systemic exposure [54].

Mechanistic refinement of apoptosis-based therapies represents another key direction. Many phytochemicals modulate BCL-2 family proteins, p53 signalling, caspase activation, and MAPK pathways [19–21,34,35]. The heterogeneity of apoptotic defects in NMSC, including BCL-2 overexpression in BCC and *TP53* mutations in cSCC, indicates that personalized combinations of phytochemicals or nano-enhanced formulations may be required to overcome resistance mechanisms [22–24]. Mapping apoptotic vulnerabilities in patient-derived NMSC samples will help identify optimal phytochemical combinations capable of restoring apoptosis [25,26]. Synergistic strategies combining phytochemicals with existing therapies warrant systematic investigation. Evidence shows that resveratrol enhances the apoptotic efficacy of ALA-PDT [46], and similar interactions may exist between phytochemicals and Hedgehog inhibitors, EGFR inhibitors, or immunotherapies [6,7]. Rational combination regimens could reduce required doses of conventional agents, lowering toxicity while maintaining therapeutic efficacy [3,5].

In vivo validation remains a critical gap in the field. Although several phytochemicals demonstrate strong pro-apoptotic activity in vitro, only a limited number have been evaluated in animal models of NMSC [30,36,55]. Future research should prioritize in vivo studies assessing pharmacokinetics, biodistribution, long-term safety, and therapeutic outcomes using UV-induced carcinogenesis and immunocompetent models [10,13]. Clinical translation will require standardized formulations, reproducible manufacturing, and rigorous safety evaluation. Variability in plant extract composition, differences in extraction methods, and instability of active constituents pose challenges for regulatory approval [37,39]. Nanoformulations must also meet criteria for biocompatibility,

biodegradability, and long-term safety, particularly for chronic or repeated topical use [53,54]. Establishing standardized protocols for phytochemical characterization and nanoformulation quality control will be essential for advancing these agents toward clinical trials [57,58].

Overall, future research should integrate mechanistic apoptosis studies, advanced nanodelivery systems, synergistic therapeutic combinations, and robust *in vivo* validation to develop safe, effective, and clinically translatable phytochemical-based therapies for NMSC. The convergence of molecular oncology, natural product pharmacology, and nanotechnology offers a promising path toward next-generation treatments capable of addressing the growing global burden of NMSC [2,10,51].

7. Conclusions

This review consolidates current evidence showing that plant-derived products with pro-apoptotic activity hold meaningful potential for advancing the treatment of non-melanoma skin cancer. Their selective cytotoxicity, ability to modulate intrinsic and extrinsic apoptotic pathways, and favorable safety profiles distinguish them from many conventional agents. Nanoformulation technologies further strengthen their therapeutic relevance by improving solubility, stability, and cutaneous penetration, enabling higher local concentrations and more consistent biological activity. Integration of mechanistic insights, optimized delivery systems, and rational combination strategies may accelerate the development of clinically viable phytochemical-based interventions. Continued refinement of nanodelivery platforms, together with rigorous in vivo validation, will be essential for translating these agents into effective and accessible therapeutic options for patients with NMSC.

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