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REVIEW

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A review on the pathogenesis of cutaneous non-melanoma skin cancer (NMSC) and selected herbs as chemoprotective agents

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ABSTRACT

The high incidence of NMSC (non-melanoma skin cancer) and the side effects of the available treatments disrupt the quality of life in more than one way. Particularly in the later stages, pain management and palliative care is the sole mean of alleviating the agony, all this warrants the need for alternative strategies with enhanced efficacy, better tolerance, and wide safety margins. Therefore, herbs in NMSC prevention and intervention are engaging due to their accessibility, efficacy, cost-effectiveness, and tolerated nature. Various components in the crude extracts follow 'Pharmacodynamic synergy', augment the beneficial effects of the active constituents, and reduce the likelihood of drug resistance. The extracts/active constituents of *Azadirachta indica*, *Catharanthus roseus*, *Ocimum sanctum*, *Phyllanthus emblica*, *Santalum album*, *Tinospora cordifolia*, and *Withania somnifera* demonstrated the anti-cancerous effect on distinct cancerous cells and animal models. Nonetheless, there is a lack of in vivo investigations validating its chemopreventive efficacy in experimental models of skin carcinogenesis. Therefore, the current review suggests the scientific community emphasize the extensive research on these herbs to obtain an efficacious drug as well as the people around the globe incorporate these herbs in their daily dietary habits/meals to obtain maximum benefit from these herbs.

List of Abbreviations

ACC1: Acetyl-CoA carboxylase 1
Akt/PI-3K: Ak strain transforming/phosphoinositide 3-kinases
AP-1: Activator protein 1
ATM: Ataxia telangiectasia mutated
BCC: Basal cell carcinoma
BRAF: v-Raf murine sarcoma viral oncogene
CAT: Catalase
CDK4: Cyclin-dependent kinase-4
CDKN2A: Cyclin-dependent kinase inhibitor 2A
CDKN2A: Cyclin-dependent kinase inhibitor 2A
CEA: Carcinoembryonic antigen
COX-2: Cyclooxygenase 2
CYP: Cytochrome P450

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DMBA: 7,12-dimethyl Benz(a)anthracene
DTD: D-Tyr-tRNATyr deacylase
ECM: Extracellular matrix
EDC: Electrodesiccation and curettage
EMT: Epithelial-mesenchymal transformation
ERBB4: Erb-b2 receptor tyrosine kinase 4
FBXW7: F-Box and WD repeat domain containing 7
GAGs: Glycosaminoglycans
Gli1/Gli: GLI family zinc finger 1/GLI family zinc finger 2
GPX: Glutathione peroxidase
GR: Glutathione reductase
GRIN2A: Glutamate receptor ionotropic NMDA type subunit 2A
GRM3: Glutamate metabotropic receptor 3
GRM8: Glutamate metabotropic receptor 8
GSH: Glutathione
Ha-ras/ Ki-ras: Harvey ras/Kirsten ras
IDH1: Isocitrate Dehydrogenase 1
JAK-STAT: Janus kinase/signal transducers and activators of transcription
KEAP1: Kelch-like ECH associated protein 1
KIT: KIT proto-oncogene, receptor tyrosine kinase
KNSTRN: Kinetochore localized astrin (SPAG5) binding protein
LDH: Lactate dehydrogenase
LPO: Lipid peroxidation
MAPK1/2: Mitogen activated protein kinase 1/2
MSC: Melanoma skin cancer
mTOR: Mammalian target of rapamycin
NF-κB: Nuclear factor kappa light chain enhancer of B cells
NMSC: Non-melanoma skin cancer
NRAS/N-ras: Neuroblastoma RAS viral oncogene homolog
ODC: Ornithine decarboxylase
PN: Peroxynitrite
POC: People of color
PREX2: Phosphatidylinositol 3,4,5-trisphosphate-dependent Rac exchanger 2
PTCH1: PATCHED1
RAC1: Ras related C3 botulinum toxin substrate 1
RUNX1T1: RUNX1 partner transcriptional co-repressor 1
SCC: Squamous cell carcinoma
SMO: Smoothened (frizzled class receptor)
SOD: Superoxide dismutase
SPF: Sun protection formula
STAT 1: Signal transducer and activator of transcription 1
STAT3: Signal transducer and activator of transcription 3
SUFU: Suppressor of fused protein
TYR: Tyrosine
UDP-GT: Uridine diphosphate glucuronyl transferase
UV: Ultraviolet
α-MSH: Alpha-melanocyte-stimulating hormone

1. Introduction

Skin cancers, including melanoma skin cancer (MSC) and non-melanoma skin cancer (NMSC), are frequent in Caucasians, and their incidence is steadily increasing worldwide (Bray et al., 2018; Labani et al., 2021). Figure 1 portrays the different types of skin cancers along with risk factors contributing to the onset of skin cancers. The high incidence of skin cancers imposes a burden on the healthcare system as well as the patient via associated morbidity, social impact, and healthcare cost (Fitzmaurice et al., 2017). Although people of color (POC) are less afflicted, they are more likely to die from skin cancers owing to the scarcity of awareness, late-stage diagnosis, and socioeconomic barriers hampering access to care (Gupta et al., 2016).

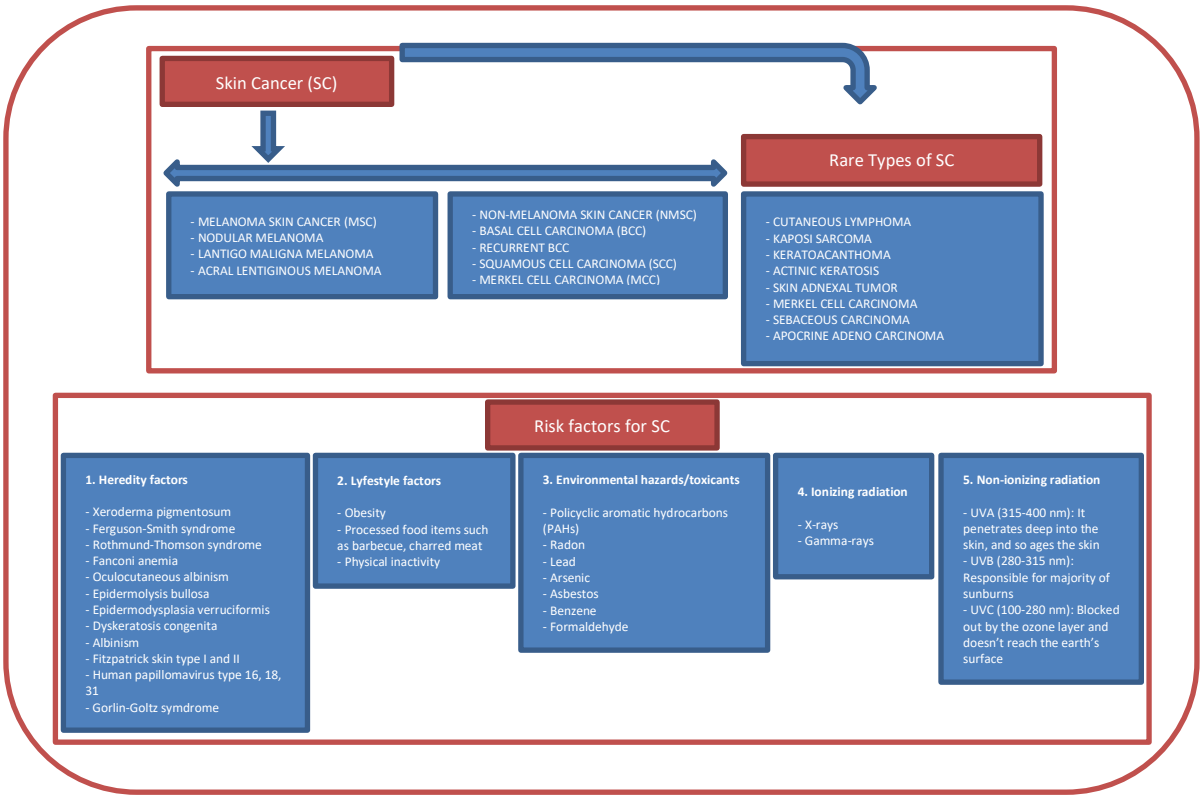

Figure 1. Different types of skin cancers (common and rare) and various risk factors responsible for the onset of skin cancer

Possible causes of NMSC pathogenesis include exposure to ultraviolet (UV) radiation, ionizing radiations, environmental toxicants/pollutants, lifestyle habits, toxic xenobiotics such as radon, lead, arsenic, polycyclic aromatic hydrocarbons (PAHs), and hereditary factors (Didona et al., 2018; Rees et al., 2014). Although site-specific treatments are effective in skin cancer, they have some limitations (aesthetic issues viz., pigmentary changes, atrophy, fibrosis, and cost burden) (Sobanko et al., 2015). Modulations in signaling pathways, high mutational burden, as well as increased risk among immunosuppressed patients led to a new landscape in skin cancer therapeutics such as epidermal growth factor receptor (EGFR) therapy, inhibitors of hedgehog signaling, BRAF, and MEK, checkpoint inhibitors, and immunotherapy such as intratumoral, oncolytic viral therapy, non-viral oncolytic therapy (Cives et al., 2020). The treatments available for metastatic tumors have many adverse effects such as weakened immunity, hair/weight loss, fatigue, sleep disturbances, fertility problems, morbidity, psychological problems in cancer survivors, and decreased quality of life. It is noteworthy that even after several therapy sessions, a high relapse rate (due to inevitable exposure to UV radiation, environmental toxicants, and chemoresistance) brings a financial burden along with significant morbidity to the patient (Sloan & Gelband, 2007). In Australia, treatment of skin cancer accounts for AUS$ 511 million in 2010 (Gordon et al., 2018). According to United States statistics, the usual annual amount of treatment for skin cancers is doubled within five years (Wu et al., 2015). Thus, there is a desperate demand for complementary treatment with minimum or nil side effects. Herbal remedies have long been used since ancient times to tackle diverse ailments, due to their easy accessibility, safe nature, effectiveness, and no toxicity (Lengai et al., 2020; Thomasset et al., 2007). Currently, we are focusing on the pathogenesis of NMSC, and alternative herbal remedies to combat the NMSC, as well as the role of selected herbs as an adjuvant along with the conventional therapies to reduce its side effects.

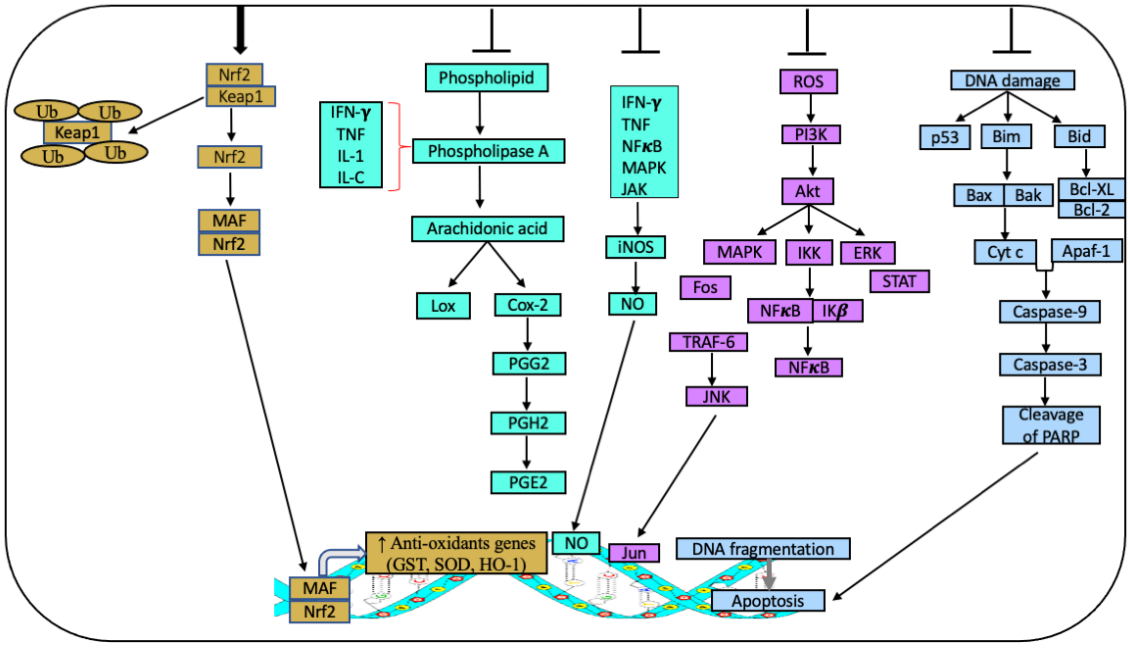

Figure 2. Mechanism of chemopreventive action of selected herbs against NMSC

Several authors have already discussed the protective role of botanicals/phytochemicals such as vitamin C and E, selenium, and carotenoids, among others against skin cancers (Chaiprasongsuk & Panich, 2022; F'guyer et al., 2003; Gan et al., 2021; Ijaz et al., 2018; Katta & Brown, 2015; Millsop et al., 2013). This review will give new insights into the selected herbs, namely *Azadirachta indica*, *Catharanthus roseus*, *Ocimum sanctum*, *Phyllanthus emblica*, *Santalum album*, *Tinospora cordifolia*, and *Withania somnifera*, and the main targets of these herbs. Figure 2 portrays how these herbs modulate/inhibit various perturbed signaling pathways and impede NMSC. The reason for choosing these herbs is that these herbs are very common in Asian countries, especially India. These herbs have already shown promising chemoprotective effects against NMSC in a few in vivo studies, but there is a lack of clinical trials on these herbs. These herbs warrant extensive research for novel drug discovery.

2. Materials and methods

For the review, reports on the cell lines and animal models were searched using scientific databases (PubMed and Google Scholar) against non-melanocytic skin cancer. In the current review, the beneficial effects of chosen herbs viz., *A. indica*, *C. roseus*, *O. sanctum*, *P. emblica*, *S. album*, *T. cordifolia*, and *W. somnifera* and their active-constituents against NMSC were described. Various databases (such as PubMed and Google Scholar) were utilized to extract the pertinent information. Various combinations of major keywords included were: *Azadirachta indica*, *Catharanthus roseus*, *Ocimum sanctum*, *Phyllanthus emblica*, *Santalum album*, *Tinospora cordifolia*, *Withania somnifera*, chemoprotective, chemotherapeutic, and chemoprotection.

3. Results and discussion

NMSC, also known as "cancer of keratinocytes," is among the most common human malignancies and is mainly classified as BCC & SCC, which account for about 99% of all NMSCs (Katalinic et al., 2003). Rare forms of NMSCs are sebaceous carcinoma, apocrine adenocarcinoma, Merkel cell carcinoma, and other rare tumors (Wollina et al., 2017). Sung et al. (2021) stated that there were

1,198,073 new cases, and 63,731 deaths occurred from NMSC in 2020.

BCC is the abnormal division of mutated basal cells and is the predominant type of NMSC (Apalla et al., 2017; Koh et al., 2003). Patients with Gorlin-Goltz syndrome, Fitzpatrick skin (I and II), are at higher risk of developing BCC (Didona et al., 2018). Although BCC develops at a slower rate, it is capable of widespread tissue destruction and causes significant morbidity. Mutation in the PATCHED1 (PTCH1, a tumor-suppressor gene) is a driving force for BCC (Lauth et al., 2004). Along with that, mutations in the genes such as c-Myc, Ras, Harvey (Ha)-ras, Kirsten (Ki)-ras, cyclin-dependent kinase inhibitor 2A (CDKN2A), NRAS, TP53, GLI family zinc finger 1 (Gli1), kinetochore localized astrin (SPAG5) binding protein (KNSTRN), GLI family zinc finger 2 (Gli2), suppressor of fused protein (SUFU), or smoothened (SMO), commence to BCC (Boeckmann et al., 2020).

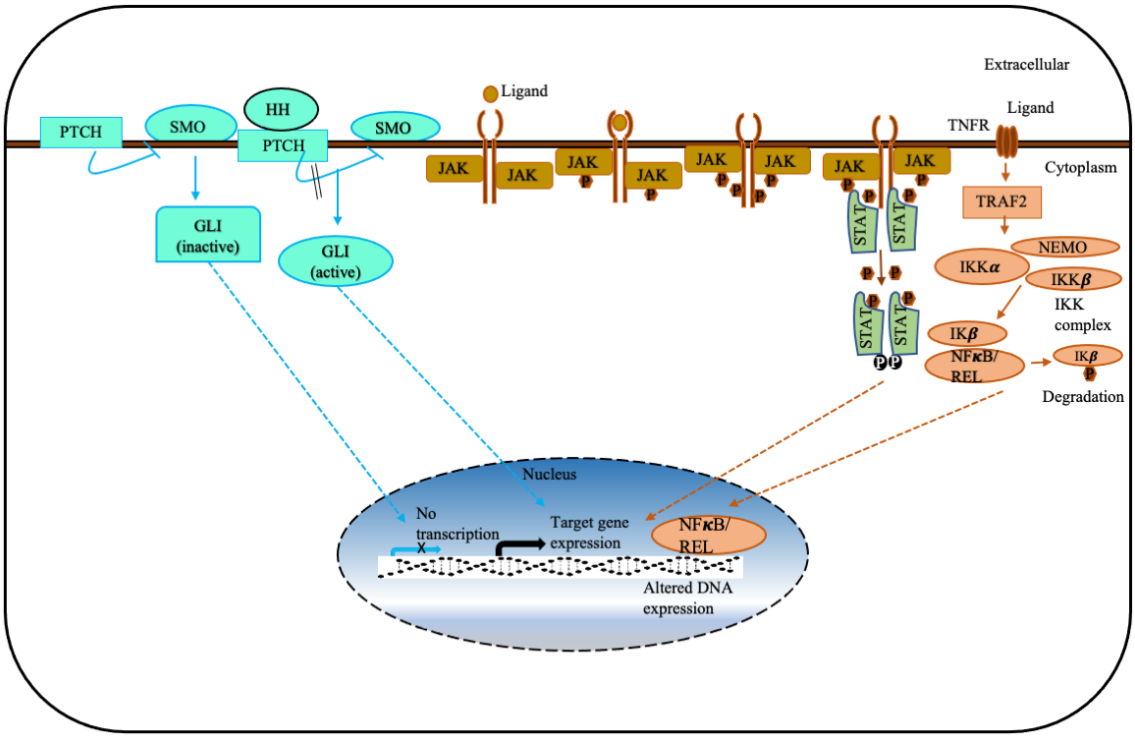

Figure 3. Various signaling pathways altered during NMSC
Mutation in the PTCH1 is a driving force for BCC.
Modulation in the JAK-STAT pathway leads to activation of NFkB signaling and commence to SCC.

SCC is the abnormal division of mutated squamous cells (Queen, 2017). Depending upon the tumor size, depth, perineural invasion, immunity of the patient, and anatomical location, SCC has enough potential for recurrence (Lee & Miller, 2009). People with human papillomavirus, Fitzpatrick skin type I and II, xeroderma pigmentosum, and albinism (Didona et al., 2018) are at higher risk of developing SCC. Almost 55% of SCC develops in the area of the head and neck, 18% on the hands and forearms, and 13% on the legs (Apalla et al., 2017; Leiter et al., 2017). Mutations in the genes such as p53, glutamate receptor 8 (GRM8), ERBB4, RUNX1 partner transcriptional co-repressor 1 (RUNX1T1), Kelch-like ECH-associated protein 1 (KEAP1), and F-box leads to SCC. In addition, mutations in the WD repeat domain containing 7 (FBXW7), and KRAS causes SCC (Kan et al., 2010). Figure 2 portrays the dysregulated signaling pathways connected to NMSC.

The side-effects of surgery (the gold standard for resecting primary skin tumors), and other treatments (Mohs micrographic surgery, curettage, and electrodesiccation) compel investigators for innovative complementary remedies with minimal adverse effects. The cost burden of the conventional modalities warrants the need for cancer prevention by primary prevention (abolishing contact with the carcinogen) or secondary prevention (repairing the already built pathologies) (Seite et al., 2017). Also, healthy individuals have the likelihood of evolving skin cancer owing to continuous exposure to UV rays exposure and environmental pollutants. Since it is impossible to avoid sun exposure, dietary habits and chemoprevention through natural products could effectively prevent skin cancer (Stoj et al., 2022).

3.1. Herbs as chemoprotective agents for NMSC

Cancer chemoprevention involves preventing, inhibiting, or reversing carcinogenesis by administering chemically synthesized or natural agents (George et al., 2021). Chemically synthesized drugs exert positive effects; however, in a long run, they instigate detrimental effects, which warrants the need to utilize the diverse medicinal potential of natural agents/herbal medicines, which are easily accessible, and considered safe, and cost-effective, for cancer management. Skin cancer involves three stages viz., initiation, promotion, and progression (Arora & Koul, 2014). Thus, the complexity of cancer can be tackled by using herbs in the form of galenical preparations (tincture, extracts, tonic) or as active components that target multiple deranged pathways. Galenical preparations follow 'pharmacodynamic synergy', in which the presence of numerous components acts in synergism and enhances the medicinal effects of active components as well as antagonizes its toxicity (Arora & Koul, 2014). It is revealed that 80% of developing nations utilize traditional medicine (Anquez-Traxler, 2011). Also, alternative medicine is gaining popularity as a complementary way of care in developed countries (Deng & Cassileth, 2013). Most

people look for substitutes that can be easily integrated into their diet to cure their illnesses (Naja et al., 2015).

Herbs, along with serving as a food and medicine for generations, also hold a unique place under modern-day "nutraceuticals" to manage high cholesterol, osteoporosis, diabetes, arthritis, diminished memory, and constipation among others along with showing anti-cancer effects (Hussain et al., 2015). Active components present within herbs such as flavonoids, terpenoids, polyphenols, carotenoids, catechins, anthocyanins, etc. have beneficial properties (Alzohairy, 2016; Guldiken et al., 2018). The next section discusses the importance of selected herbs in preventing/combating NMSC. Figure 3 shows the various phytochemicals isolated from these herbs.

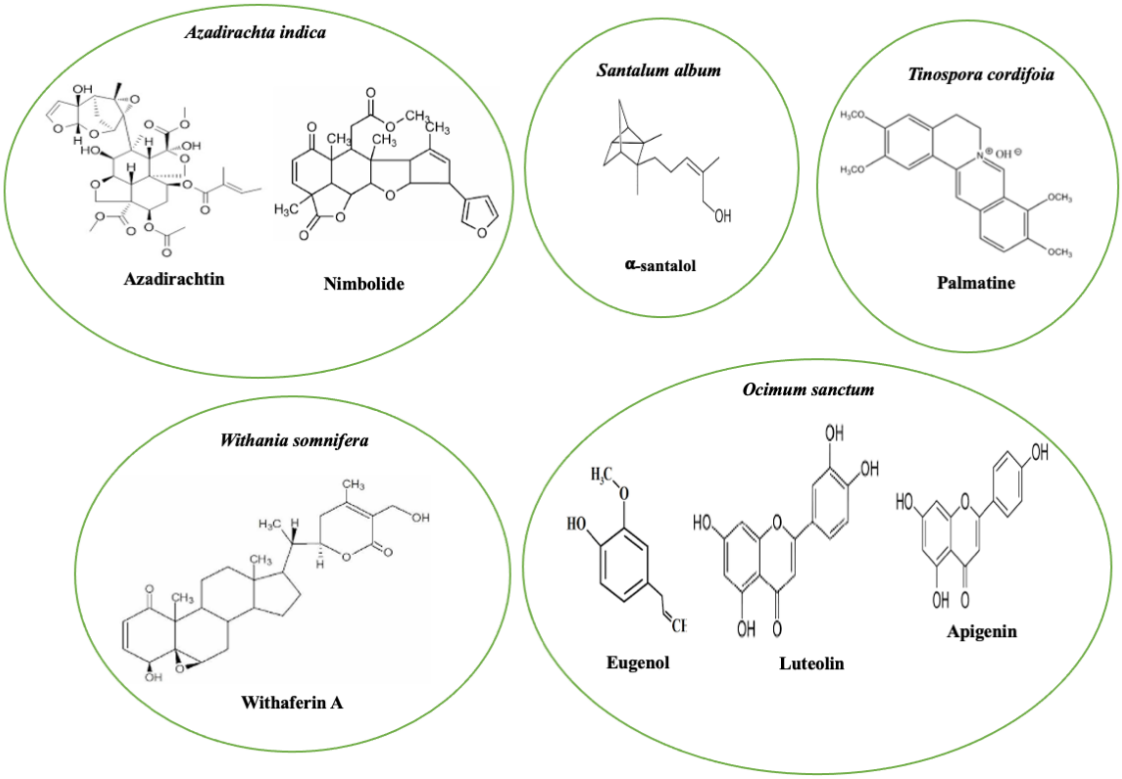

Figure 4. Active phytochemicals from selected herbs and their chemical structure

3.1.1. A. indica (Neem)

A. indica (Meliaceae) is indigenous to India, Pakistan, Burma, Nepal, and Bangladesh. *A. indica* defends the skin from harmful UV rays and other chemical contaminants, as well as skin infections and wounds (Treichel et al., 2020). The vitamins and fatty acids found in neem help minimize wrinkles and fine lines on the skin and provide an anti-aging benefit. Dasgupta et al. (2004a) reported the chemoprotective effect of *A. indica* leaves against dimethylbenz[a]anthracene (DMBA)-induced papilloma formation by increasing the antioxidant defense mechanism in albino mice. Koul et al. (2006) found that aqueous *A. indica* leaf extract (AAILE) reduced the tumor statistics, significantly improved the antioxidant enzymes in DMBA-treated mice, and thus prevented skin carcinogenesis in mice. Akihisa et al. (2009) observed that limonoids treatment to the B16 melanoma cells as well as TPA-treated mice markedly inhibited melanin production as well as decreased the inflammation in TPA-treated mice. Akihisa et al. (2011) further observed that limonoids, salanin, and 3-deacetylsalanin caused a significant reduction in melanin content in B16 melanoma cells, and markedly alleviated the inflammation in TPA-treated mice. Arora et al. (2011a) reported that AAILE treatment caused a significant improvement in skin histology and surface structure as revealed through scanning electron microscopy, and also modulated the STAT-1, AP-1, and NFkB genes expression in DMBA/TPA treated mice. Further, they also found that AAILE treatment caused a marked reduction in tumor incidence, tumor burden, and tumor volume. Also, AAILE treatment caused a significant increase in apoptosis of cancerous cells as revealed via expressions of Bcl-2, Bax, caspase-9, and caspase-3 (Arora et al., 2011b). Arora et al. (2013) also showed in a study that AAILE treatment significantly decreased the cytochrome p450 levels, and increased the DTD, UDP-GT, and LPO in skin/tumors, and liver tissues of tumor-bearing mice, which showed its chemopreventive effect. Arora et al. (2013) also found that AAILE caused a significant decrease in PCNA, and cyclin D1, which are cell-cycle proteins responsible for cell proliferation. Also, AAILE treatment caused markedly increased expressions of p53 and p21. Ali et al. (2015) observed that stigmasterol treatment had a chemopreventive effect against DMBA/croton oil-induced skin cancer in mice as revealed via the reduction in tumor size, number, decreased DNA damage, and increase in antioxidant enzymes. Chugh et al. (2018) observed that AAILE treatment caused a marked reduction in skin papilloma formation as unveiled via scrutinizing the cell proliferation, cell count, DNA/amide ratio, ODC, ATM, and LDH within skin/papilloma of mice. After that, Chugh and Koul (2021) observed that AAILE treatment decreased the GAGs levels, collagen levels, and CEA levels, and thus modulated the ECM to reduce the metastasis of skin carcinoma in the DMBA/TPA-induced murine skin cancer model. Table 1 lists a few findings validating its protective role against NMSC.

3.1.2. C. roseus (Sadabahaar)

C. roseus, also known as "periwinkle" (Apocynaceae), is indigenous to Madagascar, hence the name "Madagascar periwinkle." Now, it is available in almost all of the world's warm areas. It has found a role in both western medicine and traditional therapies and has shown extensive health benefits. Ayurvedic physicians used the flowers of *C. roseus* to treat eczema, dermatitis, and other skin issues (Nayak & Pinto Pereira, 2006). Pham et al. (2018) observed that *n*-butanol extract of *C. roseus* caused significant cytotoxicity on *Escherichia coli* and *Staphylococcus lugdunensis*. Rezadoost et al. (2019) showed that methanolic extract of *C. roseus* significantly increased the apoptosis of MCF-7, A431, and U87-MG cancerous cells. Pham et al. (2019) also observed that the root extract of *C. roseus* markedly inhibited the growth of *E. coli*, *Enterobacter aerogenes*, *S. lugdunensis*, *Candida albicans* , and *Aspergillus* spp. Table 2 lists a few findings validating its protective role against NMSC.

Table 1. Different reports on the chemoprotective efficacy of *A. indica* against NMSC

Extract/active component	Cell line/animal model	Dose	Duration	Effects	Mechanism of action	References
Ethanolic extract of *A. indica* leaves	DMBA-induced skin papilloma genesis in Swiss albino mice	250 and 500 mg per kilogram (kg) body weight (bw)	for 15 days	Chemopreventive	↑ Phase-II enzyme ↑GST, DT-diaphorase (in extrahepatic), GR (in extrahepatic), GPX, SOD, and CAT ↓ Tumor incidence/burden, number of papilloma ↑ Antioxidant enzymes	(Dasgupta et al., 2004a)
Aqueous *A. indica* leaf extract (AAILE)	DMBA-induced skin tumors in male mice	400 mg/kg bw	for 14 weeks	Chemopreventive	↓ Mean tumor burden and tumor volume, CAT, SOD ↑LPO, GSH, GPx, and GR ↓ Mean tumor burden, tumor volume, & hyperchromatia ↑LPO	(Koul et al., 2006)
Limonoids from seed extract of neem	B16 melanoma cells 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation in mice	25 mg/ml	for 20 weeks	Anti-inflammatory & Chemopreventive	↓ Melanin production (74–91%) ↓ Inflammation ↓ Epstein-Barr Virus Early Antigen (EBV-EA)	(Akihisa et al., 2009)
Several limonoids from *n*-hexane extract of Neem seeds Salanin and & 3-deacetylsalanin	B16 melanoma cells & TPA-induced inflammation in mice	25µg/ml	for 3 hours	Cytotoxic as well as anti-inflammatory	70-74% reduction in melanin content 79-85% cell viability 2,3,5,6, and 9-15 showed marked anti-inflammatory activity	(Akihisa et al., 2011)
Aqueous *A. indica* leaf extract (AAILE)	Skin carcinogenesis in LACA mice by topical application of DMBA followed by TPA	300mg/kg bw	On alternate days	Chemopreventive	↑ Regions of degeneration in histology & SEM ↑ STAT 1 and AP-1 ↓ NF-κB	(Arora et al., 2011a)
Aqueous *A. indica* leaf extract (AAILE)	Skin carcinogenesis in mice	300mg/kg bw	for 20 weeks	Apoptotic	↓ Tumor incidence (58.3%), mean tumor burden (54.5%), and mean tumor volume (45.6%) ↑ Bax, caspase 3, caspase 9 ↓ Bcl-2	(Arora et al., 2011b)
Aqueous *A. indica* leaf extract (AAILE)	Effect of skin carcinogenesis induced by DMBA/TPA on skin and hepatic tissue's biochemical status in mice	300mg/kg bw	for 10 weeks	Anti-cancer	↓ Cytochrome p450 (CYP) & GSH level (in liver & skin) ↑ DTD, UDP-GT (in liver & skin), and UDP-GT activity (in liver) ↑ LPO (in liver & skin)	(Arora et al., 2013)
Aqueous *A. indica* leaf extract (AAILE)	Skin carcinogenesis induced by DMBA/TPA in male LACA mice	300mg/kg bw	for 20 weeks	Chemopreventive	↓ PCNA and cyclin D1 ↑ p53 and p21 ↑ LPO	(Arora et al., 2013)
Stigmasterol from *A. indica*	DMBA/Croton oil-induced skin cancer in mice	200 mg/kg and 400 mg/kg bw	for 16 weeks	Chemopreventive	↑ Latency period ↓ Tumor size, number of papillomas, LPO, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and bilirubin ↓ DNA damage ↑ Glutathione, SOD, and CAT	(Ali et al., 2015)
Aqueous *A. indica* leaf extract (AAILE)	DMBA/TPA-induced skin papilloma genesis in mice	300mg/kg bw	for 10 weeks	Growth inhibitory	↓ Papilloma incidence and number ↓ Cell proliferation, epidermal thickness & cell count, DNA/amide I ratio ↓ ODC, ATM ↓ LDH	(Chugh et al., 2018)
Aqueous *A. indica* leaf extract (AAILE)	DMBA/TPA-induced skin cancer in mice	300mg/kg bw	for 22 weeks	Chemopreventive	↓ Collagen and glycosaminoglycans (GAG) levels ↓ Carcinoembryonic antigen (CEA)	(Chugh & Koul, 2021)

Table 2. Different reports on the chemoprotective efficacy of *C. roseus* against NMSC

Extract/active component	Cell line/animal model	Dose	Duration	Effects	Mechanism of action	References
Extract of *C. roseus* stem & its *n*-butanol fraction	A2780 (ovarian), H460 (lung), A431 (skin), MIA PaCa-2 (pancreas), Du145 (prostate), HT29 (colon), MCF-7 (breast), BE2-C (neuroblastoma), SJ-G2, U87, and SMA (glioblastoma)	GI_{50} values of 5.2-21.0 µg/ml	for 0-72 hours	Cytotoxic	↓ Activity of *E. coli* & *S. lugdunensis*	(Pham et al., 2018)
Methanolic extract of *C. roseus*	MCF-7 breast cancer cells, A431 epidermal cell line, and U87-MG glioma cell line that were compared to HGF-1 as normal cells	50 µg/ml	for 0-72 hours	Apoptotic	↑ Apoptosis of cancer cells	(Rezadoost et al., 2019)
C. roseus root extract (RE) and its sub-fractions: saponin-enriched (SE) and aqueous (AQ) fractions	A2780 (ovarian), H460 (lung), A431 (skin), MIA PaCa-2 (pancreas), Du145 (prostate), HT29 (colon), MCF-7 (breast), BE2-C (neuroblastoma), SJ-G2, U87, and SMA (glioblastoma)	100 µg/ml	for 0-72 hours	Antioxidative & growth inhibitory	↓ Growth of *E. coli*, *E. aerogenes*, and *S. lugdunensis* and fungi (*C. albicans* and *A. niger*)	(Pham et al., 2019)

Table 3. Different reports on the chemoprotective efficacy of *O. sanctum* against NMSC

Extract/active component	Cell line/animal model	Dose	Duration	Effects	Mechanism of action	References
Apigenin	DMBA-initiated and TPA promoted skin tumorigenesis in SENCAR mice	1 to 20 µmol	for 33 weeks	Chemopreventive	↓ Tumor incidence ↓ ODC ↓ Papilloma incidence and numbers ↑ Latency period of tumor appearance ↓ Incidence of carcinoma, & numbers ↓ Ratio of carcinomas/papilloma	(Wei et al., 1990)
Eugenol	DMBA-induced and croton oil promoted	2 mg	for 6 weeks	Free-radical scavenging	↓ SOD, LPO ↓ Number of papillomas (84%) ↓ Number of tumor	(Sukumaran et al., 1994)
Ethanolic tulsi leaf extract	DMBA-induced skin papillomagenesis in swiss albino male mice	150 µl	for 15 days	Chemopreventive	↓ Tumor incidence (papillomas) ↓ Average number of tumors, cumulative number of papillomas ↑GSH, GST	(Prashar et al., 1994)
Ethanolic leaf extract of *O. sanctum*	DMBA/ croton oil-induced papillomagenesis in the skin of male Swiss albino mice	800 mg/kg bw	for 15 days	Chemopreventive	↓ Number of tumor, cumulative number of papillomas, and mean number of tumors ↑GST ↑ Glutathione level	(Prashar & Kumar, 1995)
Apigenin	UVB-induced skin carcinogenesis in mice	5 µM/200 µl DMSO 10 µM (0-100 µM)	for 11 weeks	Chemopreventive	↓ ODC (25-45% inhibition) activity ↓ Cancer incidence (52% inhibition) ↑ Tumor free survival	(Birt et al., 1997)
Hydroalcoholic extract of the fresh leaves of Tulsi	Benzo(a)pyrene-induced forestomach and DMBA-initiated skin papilloma genesis in mice	200 and 400 mg/kg bw	for 15 days	Chemopreventive	↑ Phase II enzymes, GST, DT-diaphorase, GR, SOD, GSH, and CAT in hepatic and extrahepatic organs ↑ GST and DT-diaphorase (in forestomach, kidney, and lung) ↓ Phase I enzyme, LPO and LDH ↓ Tumor burden, percentage of tumor bearing-animals	(Dasgupta et al., 2004b)
Alcoholic extract of the Tulsi leaves	Carcinogens viz., 3-mthylcholanthrene (MCA), DMBA and aflatoxin B1 (AFB1)-initiated TPA promoted by following 2-stage Skin tumorigenesis in a mouse model	100 µl	for 24 weeks	Antiproliferative Immunomodulatory & antioxidant	↓ Number of tumors ↓ Cutaneous γ-glutamyl transpeptidase (GGT) and glutathione-*S*-transferase-P (GST-P) ↑ Infiltration of polymorphonuclear, mononuclear and lymphocytic cells ↓ ODC activity ↑ Interleukin-1β (IL-1β), TNF-α (serum) ↓ Phase I enzymes ↑Phase II enzymes ↑ Glutathione levels ↓ LPO, heat shock protein	(Rastogi et al., 2007)

Extract/active component	Cell line/animal model	Dose	Duration	Effects	Mechanism of action	References
Apigenin	UVB-induced mouse and human 308 keratinocyte cell line	5-50 µM	for 22 hours	Chemopreventive	↓ COX-2	(Van Dross et al., 2007)
Luteolin	UV-induced skin cancer & JB6 P+ cell line and the SKH-1 hairless mouse model	10 or 20 µmol/l	for 0-12 hours	Chemopreventive	↓ Protein kinase C (epsilon), c-Src activities, activator protein-1, and nuclear factor-κB activity ↓ Phosphorylation of mitogen-activated protein kinases and the Akt signaling pathway ↓ Tumor incidence,multiplicity, and overall size ↓ Cyclooxygenase-2, tumor necrosis factor-α, PCNA, PKCε, and Src kinase	(Byun et al., 2010)
Eugenol	DMBA initiated and TPA promoted skin tumorigenesis	30 µL	for 28 weeks	Antiproliferative, anti-inflammatory, & antioxidative	↓ Oxidative stress, inflammation, cell proliferation ↑ Apoptosis ↓ IL-6, TNF-α, and PGE_2 ↓ NF-κB	(Kaur et al., 2010)
Luteolin	UV-induced damages in human keratinocytes in vitro, ex vivo, and in vivo	12 µg/mL	for 0-24 hours	Antioxidative & anti-inflammatory	↓ Cyclobutane pyrimidine dimers ↓ Skin erythema ↓ Cyclooxygenase-2, prostaglandin E_2 production	(Wölfle et al., 2011)

3.1.3. *O. sanctum* (Tulsi)

O. sanctum, also famous as "Queen of Herbs", is a member of the Labiatae family that originated in north-central India and now grows throughout the eastern world tropics (Africa, America, Asia, China). In ancient times, it was topically applied to the skin to heal acne and wounds (Marwat et al., 2011). Tulsi also protected the skin by avoiding blackheads and treating fungal infections (Khan et al., 2010) and wounds (Mandal et al., 2022). Wei et al. (1990) showed the chemopreventive efficacy of apigenin against DMBA/TPA-induced skin tumorigenesis in mice as evidenced by the reduction in tumor incidence, ODC, papilloma incidence, and carcinoma incidence. Sukumaran et al. (1994) observed that eugenol treatment caused a significant decrease in LPO, SOD, number of papillomae, and number of tumor-bearing mice and thus showed free radical scavenging potential. Prashar et al. (1994) found that ethanolic tulsi leaf extract markedly reduced the tumor incidence, and the average number of tumors, and significantly improved the activity of the antioxidant enzymes in DMBA-treated mice. Prashar and Kumar (1995) reported that ethanolic extract of tulsi caused a marked reduction in the number of tumors, papillomas, and significantly improved the GST, and GSH levels within DMBA-induced mice. Birt et al. (1997) observed that apigenin reduced the UVB-induced skin carcinogenesis in mice by reducing the cancer incidence as well as the expression of ODC in mice. Dasgupta et al. (2004b) reported that tulsi leaf extract significantly improved the antioxidant defense mechanism of benzopyrene-induced tumor-bearing mice. Van Dross et al. (2007) found that apigenin showed chemopreventive efficacy against UVB-induced carcinoma in mice and keratinocyte cells. Rastogi et al. (2007) observed that alcoholic extract of Tulsi enhanced the endogenous antioxidant enzymes, and decreased the number of tumors, inflammation, and ODC in tumor-bearing mice. Byun et al. (2010) found that luteolin decreased tumor incidence, tumor size, cyclooxygenase-2 activity, protein kinase C activity, and modulated the MAPK and Akt signaling in JB6 P+ cells and SKH-1 mouse model, and thus showed a chemoprotective effect. Kaur et al. (2010) stated that eugenol markedly attenuated oxidative stress, inflammation, cell proliferation, and substantially increased the apoptosis of tumor cells in DMBA/TPA treated mice. Wölfle et al. (2011) reported that luteolin decreased the formation of cyclobutene pyrimidine dimers, skin erythema, cyclooxygenase-2, and prostaglandin E2 production against UV-induced damages in keratinocytes. Table 3 lists a few findings validating the protective role of *O. sanctum* against NMSC.

3.1.4. *P. emblica* (Amla)

P. emblica, or "Indian gooseberry" (Euphorbiaceae), is indigenous to Asia, China, India, Nepal, and Sri Lanka (Ahmad et al., 2021). It has been reported that *P. emblica* reduces the UV-induced erythema and strikingly reduces the free radicals (Fujii et al., 2008). Its seeds are also used to heal scabies and itches (Mehmood et al., 2011). Amla also aids in treating freckles and age spots (Singh et al., 2012). Sancheti et al. (2005) observed that amla fruit extract decreased the tumor incidence, tumor burden, and tumor yield in DMBA/croton oil-induced skin carcinogenesis in a murine model and thus showed a chemoprotective effect. Majeed et al. (2011) showed that the amla fruit extract significantly decreased the collagen damage as well as ROS level in normal fibroblast cells exposed to UVB. Fujii et al. (2013) observed that amla extract and collagen peptide significantly reduced epidermal hyperplasia, and skin wrinkle formation in UVB-induced hairless mice. Table 4 lists a few findings validating the protective role of *P. emblica* against NMSC.

3.1.5. *S. album* (Chandan)

S. album, or "Royal Tree" (Santalaceae), is indigenous to Asia, Australia, Hawaii, and Pacific Islands (Santha & Dwivedi, 2015). Sandalwood is the most commonly utilized incense among Chinese and Japanese people (Goswami & Tah, 2018; Khan et al., 2021). The Egyptians used its wood for embalming the deceased to venerate the god (Kumar et al., 2012). Sandalwoods are under the Padma (lotus) group in Buddhism and ascribed to the bodhisattva Amitabha. It is perhaps one of the most often used scents in incense offerings to the Buddha (Goswami & Tah, 2018). In 1997, it is categorized under 'vulnerable' species by the International Union for Conservation of Nature (IUCN) (Kumar et al., 2012). *S. album* also can cure skin diseases such as pimples, scars, and eczema. Its essential oil is mainly used in Ayurvedic medicine to alleviate anxiety. This essential oil is also used for skin toning and treating skin problems. It also has anti-aging and anti-tanning properties. Alpha-santalol is the main active constituent of sandalwood oil, which showed promising anti-inflammatory, chemopreventive, and fungicidal effects (Bommareddy et al., 2019). Dwivedi and Abu-Ghazaleh (1997) showed that sandalwood oil significantly decreased the papilloma incidence, and papilloma multiplicity, and reduced the ODC expressions against DMBA/TPA-induced skin papilloma genesis in mice. Further, Dwivedi and Zhang (1999) observed that sandalwood oil reduced the papilloma incidence as well as

multiplicity in CD-1 mice. Dwivedi et al. (2003) observed that α-santalol treatment caused a marked decrement in papilloma incidence, and ODC activity in DMBA/TPA-induced mice. Dwivedi et al. (2006) found that α-santalol treatment markedly decreased the tumor incidence, ODC activity, DNA synthesis, and incorporation of 3H thymidine in DNA in DMBA/TPA treated mice. Kaur et al. (2005) showed that sandalwood oil significantly decreased the cell number, and increased the apoptosis, and autophagy of A431 carcinoma cells. Dwivedi et al. (2006) stated that α-santalol treatment markedly reduced the tumor incidence, multiplicity and ODC activity in UVB/TPA treated mice. Bommareddy et al. (2007) found that α-santalol markedly decreased the tumor multiplicity and LPO in UVB-treated female mice. Arasada et al. (2008) observed that α-santalol significantly decreased tumor incidence, multiplicity, and increased the apoptosis of mutated cells in UVB-treated mice. Zhang et al. (2010) showed that α-santalol markedly decreased the cell viability, downregulated the expression of mutated cell cycle genes, and increased the p21 expression in A431 carcinoma as well as UACC-62 melanoma cells. Chilampalli et al. (2013) observed that α-santalol markedly reduced the tumor multiplicity, cell viability, cell proliferation, and induced apoptosis in A431 carcinoma cells as well as UVB-treated mice. Dickinson et al. (2014) stated that sandalwood oil markedly decreased the PARP cleavage, and AP-1 activity, and increased the apoptosis as well as autophagy in HaCaT keratinocytes. Table 5 lists the findings that showed Sandalwood's chemopreventive efficacy against skin cancer.

Table 4. Different reports on the chemoprotective efficacy of *P. emblica* against NMSC

Extract/active component	Cell line/animal model	Dose	Duration	Effects	Mechanism of action	References
Amla fruit extract	DMBA/croton oil-induced skin carcinogenesis in mice	-	for 16 weeks	Chemopreventive	↓ Tumor incidence, tumor yield, tumor burden, cumulative number of papilloma	(Sancheti et al., 2005)
Amla fruit extrac	Human skin fibroblast cells	0-40µg/ml	for 0-48 hours	Chemopreventive	↑Cell-proliferation, TIMP-1, and production of procollagen ↓ Matrix metalloproteinase-1 (MMP-1) production	(Fujii et al., 2008)
Amla fruit extract	Normal human dermal fibroblasts exposed with UVB irradiation	0.5 mg/ml	for 0-24 hours	Photoprotective	↓ Collagen damage ↓ ROS	(Majeed et al., 2011)
Amla extract and collagen peptide	Photoaging induced by UVB irradiation in Male Hos:HR-1 hairless mice	5%	for 7 weeks	Photoprotective	↓ 8- OHdG-positive cells and epidermal hyperplasia ↓ Skin wrinkle formation in the mice	(Fujii et al., 2013)

Table 5. Different reports on the chemoprotective efficacy of *S. album* against NMSC

Extract/active component	Cell line/animal model	Dose	Duration	Effects	Mechanism of action	References
Sandalwood oil (5% in acetone, w/v)	DMBA-initiated and TPA-promoted skin papillomas in mice	100 µl	for 20 weeks	Chemopreventive	↓ Papilloma incidence by 67% & multiplicity by 96% ↓ ODC activity by 70%	(Dwivedi & Abu-Ghazaleh, 1997)
Sandalwood oil	CD-1 mice	5% pre-treated	-	Chemopreventive	↓ Papilloma incidence and multiplicity	(Dwivedi & Zhang, 1999)
α-Santalol	DMBA-initiated and TPA-promoted skin tumors in CD-1 and SENCAR mice	5%	for 20 weeks	Chemopreventive	↓ Papilloma development ↓ ODC activity ↓ Incorporation of ^{3}H-thymidine in DNA	(Dwivedi et al., 2003)
α-Santalol	DMBA-initiated and TPA-promoted skin cancer in mice	1.25% and 2.5%	for 20 weeks	Chemopreventive	↓ Tumor incidence and multiplicity ↓ ODC activity and DNA synthesis ↓ Incorporation of ^{3}H-thymidine in DNA	(Dwivedi et al., 2006)
East Indian sandalwood oil & α-santalol (about 25–75 µM)	Human epidermoid carcinoma A431 cells	25-75 mM	for 0-48 hours	Apoptotic & anti-proliferative	↓ Cell number ↑ Caspase-3, poly(ADP-ribose) polymerase cleavage, caspase-8 and caspase-9 ↓ Mitochondrial membrane potential ↑ Cytochrome C ↑ Autophagy through stimulation of microtubule-associated protein 1 light chain 3 (LC3)	(Kaur et al., 2005)
α-Santalol	UVB-induced skin tumorigenesis of SKH-1 hairless mice under three different protocols (DMBA-initiated and UVB-promoted; UVB-initiated and TPA-promoted and UVB-initiated and UVB promoted)	5%	for 30 weeks	Chemopreventive	↓ Tumor incidence and multiplicity ↓ ODC activity	(Dwivedi et al., 2006)
α-Santalol	UVB-induced skin tumour development in female SKH-1 mice	1.25%, 2.5%, and 5%	for 30 weeks	Antioxidant and anti-cancer activity	↓ Tumor multiplicity ↓ LPO (in skin and liver microsomes)	(Bommareddy et al., 2007)

Extract/active component	Cell line/animal model	Dose	Duration	Effects	Mechanism of action	References
α-Santalol	UVB-induced skin tumor development in SKH-1 mice	5%	for 30 weeks	Apoptosis	↓ Tumor incidence and multiplicity ↑ Caspase-3, caspase-8 levels, and p53 ↓ Development of tumors	(Arasada et al., 2008)
α-Santalol	Mutated human epidermoid carcinoma A431 cells and p53 wild-type human melanoma UACC-62 cells	50-100 µM 50–75 µM	for 0-72 hours	Anti-proliferative	↓ Cell viability ↑ G2/M phase cell cycle arrest ↑ Cyclin A, cyclin B1, Cdc2, Cdc25c, p-Cdc25c, and Cdk-2 ↑ p21, wild-type p53 ↓ Mutated p53 in UACC-62 cells ↑ Depolymerization of microtubules	(Zhang et al., 2010)
α-Santalol, honokiol and magnolol isolated from *Magnolia officinalis* bark extract	Chemically and UVB-induced skin cancer development in mice & humans epidermoid carcinoma A431 cells	Combination treatment of α-santalol (5 mg in 100 µl acetone) and honokiol (30 µg in 100 µl acetone)	for 30 weeks	Apoptotic	↓ Tumor multiplicity, cell viability, cell-proliferation (90% reduction) ↑ Apoptosis	(Chilampalli et al., 2013)
East Indian sandalwood oil (EISO)	HaCaT keratinocytes (UV-signature mutations, dysfunctional p53 and a defective NFkB signaling pathway)	0.0005% & 0.001%	for 0-24 hours	Anti-cancer	↓PARP cleavage ↑Apoptosis ↓ AP-1 activity ↓ Plasma membrane integrity ↑ Cleavage of LC3 ↑ Autophagy ↓ Multiplication of cells	(Dickinson et al., 2014)

3.1.6. T. cordifolia (Guduchi)

T. cordifolia, also known as "Giloy" (Menispermaceae), is abundant in South Asia, Indonesia, the Philippians, Bangladesh, Thailand, Myanmar, China, and Srilanka (Upadhyay et al., 2010). It is the best remedy for skin problems such as black spots, pimples, fine lines, wrinkles, and acne and slows down the aging process (Yates et al., 2022). Goyal et al. (2007) showed that root extract of *T. cordifolia* significantly decreased the tumor incidence, tumor yield, and tumor burden in DMBA/TPA treated mice. Chaudhary et al. (2008) showed that *T. cordifolia* extract significantly decreased the papilloma number, tumor burden, and LPO, and markedly increased the phase-II detoxifying enzymes in DMBA/croton oil treated mice. Ali and Dixit (2013) reported that palmatine significantly decreased the tumor size, and number, and significantly increased the antioxidant enzyme activities, restoring the DNA damage in DMBA/croton oil treated mice. Table 6 summarizes a few studies that demonstrated the protective potential of *T. cordifolia* against NMSC.

Table 6. Different reports on the chemoprotective efficacy of *T. cordifolia* against NMSC

Extract/active component	Cell line/animal model	Dose	Duration	Effects	Mechanism of action	References
Root extract of *T. cordifolia* plant extract (TCE)	Two-stage skin carcinogenesis process in Swiss albino mice	-	for 16 weeks	Anti-tumor	↓ Tumor incidence, tumor yield, tumor burden, and cumulative number of papillomas	(Goyal et al., 2007)
T. cordifolia extract	Two-stage skin carcinogenesis model in mouse using DMBA/croton oil	100 mg/kg bw	for 16 weeks	Anti-oncogenic	↓ Cumulative number of papillomas, tumor yield, tumor burden, and tumor weight ↑ Phase II detoxifying enzymes ↓ LPO	(Chaudhary et al., 2008)
Alkaloid palmatine extracted from *T. cordifolia*	DMBA/croton oil induced skin carcinogenesis in Swiss albino mice	200 mg/kg bw	for 16 weeks	Anticancer	↓ Tumor size, number ↑ GSH, SOD, CAT, restored the increased DNA damage	(Ali & Dixit, 2013)

3.1.7. W. somnifera (Ashwagandha)

Ashwagandha, or "Indian ginseng" (Solanaceae), is grown in Afghanistan, India, Egypt, Morocco, Nepal, Sri Lanka, China, Jordan, Congo, Baluchistan, South Africa, and Yemen (Mandlik & Namdeo, 2021). Ashwagandha benefits the skin by replenishing natural oils and creating skin-enriching compounds such as hyaluronan, elastin, and collagen, giving skin hydration and suppleness, and strength. Davis and Kuttan (2001) showed that 1-oxo-5b, 6b-epoxy-with a-2-enolide isolated from the chloroform root extracts of *W. somnifera* markedly enhanced the antioxidant enzyme activities, and decreased the LPO in DMBA-treated mice. Prakash et al. (2002) reported that hydroalcoholic root extract of *W. somnifera* markedly decreased the incidence as well as the number of skin tumors, and enhanced the antioxidant enzyme activities in DMBA-treated mice. Mathur et al. (2004) found that 1-oxo-5b, 6b-epoxy-with a-2-enolide isolated from the chloroform root extracts of *W. somnifera* markedly increased the p53 foci in UVB exposed rats, and thus showed anti-cancerous activity. Padmavathi et al. (2005) showed that *W. somnifera* root extract significantly decreased the phase I xenobiotic metabolizing enzymes, and increased the phase II antioxidative enzymes, decreased the tumor incidence, and multiplicity in benzopyrene and DMBA treated mice. Li and Zhao (2013) showed that withaferin A markedly decreased cell proliferation, LDH, and IDH-1, and increased the mitochondrial membrane potential, complex-I activity, and mitochondrial respiration in JBP6+ cells as well as TPA-treated mice. Maliyakkal et al. (2015) found that ethanolic extracts of *W. somnifera* (WS-ET) and *T. cordifolia* markedly decreased the side population, ABC-B1, and ABC-G2 transporters in CSCs. Li et al. (2016) showed that withaferin A attenuated the cell proliferation, ACC-1, and AP-1 and thus showed a chemopreventive effect against chemically induced skin

carcinogenesis in the murine model. Xu et al. (2019) observed that withaferin A decreased tumor promotion via stabilizing the IDH-1, and inactivating HIF-1A in TPA-treated mice. Table 7 lists a few findings that indicate the protective role of Ashwagandha against NMSC.

Table 7. Different reports on the chemoprotective efficacy of *W. somnifera* against NMSC

Extract/active component	Cell line/animal model	Dose	Duration	Effects	Mechanism of action	References
W. somnifera	DMBA-treated group	20 mg/kg bw i.p.	-	Anti-cancer	↓ LPO ↑ GSH, GST, GPx, and CAT	(Davis & Kuttan, 2001)
W. somnifera hydroalcoholic root extract (WSRE)	DMBA-induced skin cancer in mice	400 mg/kg orally	-	Chemopreventive	↓ Incidence and an average number of skin lesions ↑ GSH, LPO, SOD, CAT, GPX, and GST ↓ MRN complex protein NBS-1	(Prakash et al., 2002)
1-*oxo*-5b, 6b-epoxy-with a-2-enolide isolated from the chloroform root extracts of *W. somnifera*	Skin tumors in rats by UVB radiation followed by topical treatment with benzoyl peroxide	20 mg/kg bw	for 12 weeks	Anti-cancer	↑ p53+foci (clusters of cells containing the mutated p53 protein)	(Mathur et al., 2004)
W. somnifera root extract	Benzo(a)pyrene-induced forestomach papilloma genesis and DMBA-induced skin papilloma genesis in the Swiss albino mice	2.5% and 5% (w/w)	for 14 days	Chemopreventive	↓ Phase I xenobiotic metabolizing enzymes ↑ Phase II and Antioxidant enzymes (liver) ↓ Tumor incidence and multiplicity (in stomach and skin) ↓ MDSC ↓ Metastasis of tumor	(Padmavathi et al., 2005)
Withaferin A (WA)	Skin epidermal JB6 P+ cells, a well-established TPA model for tumor promotion in mouse	20 µg	-	Chemopreventive	↓ Cell proliferation ↓ LDH & isocitrate dehydrogenase 1 (IDH1) ↑ Mitochondrial membrane potential, complex I activity and mitochondrial respiration ↑ α-Ketoglutarate	(Li & Zhao, 2013)
Ethanolic extracts of *W. somnifera* (WS-ET) and *T. cordifolia* (TC-ET)	Cancer stem cells (CSCs)	WS-ET (20 µg/ml) and TC-ET (50 µg/ml)	for 0-96 hours	Tumor sensitizing & cytotoxic	↓ Side-population (SP), ABC-B1, and ABC-G2 transporters	(Maliyakkal et al., 2015)
Withaferin A	Chemically-induced skin carcinogenesis mouse model	20 µg	for 14 weeks	Chemopreventive	↓ Cell proliferation, acetyl-CoA carboxylase 1 (ACC1), activator protein (AP) 1	(Li et al., 2016)
Withaferin A	TPA-induced skin cancer	-	-	Chemopreventive	↓ Tumor promotion via stabilizing IDH1, & inactivating HIF-1α signaling	(Xu et al., 2019)

3.2. Challenges faced by herbs

The major challenge is the lack of pharmacokinetics studies (absorption, distribution, metabolism, excretion, and toxicity profile) on these herbs, and only a few pre-clinical studies on the defending efficacy of these plants against NMSC are present, that's why these herbs have not been used in clinical trials till date. This review draws the attention of scientists worldwide to explore these herbs for the discovery of new medicines. Also, this review emphasizes the importance of these herbs and suggests that people worldwide get the maximum benefit from these herbs by incorporating them into daily food. Combining traditional and pharmacological expertise could lead to new, less expensive, and potentially successful anticancer drugs.

4. Conclusions

In conclusion, the above-discussed herbs showed promising anti-cancerous efficacy against cell lines and animal models. However, there is a need for extensive research on different parts of these herbs viz., leaf, stem, root, seed, etc. to bring these herbs into clinical trials and further isolation of active phytochemicals for the discovery of safer drugs.

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The authors declare that they have no potential conflict of interest.

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Supplementary File

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References

Ahmad, B., Hafeez, N., Rauf, A., Bashir, S., Linfang, H., Rehman, M. U., Mubarak, M. S., Uddin, M. S., Bawazeer, S., *et al.* (2021). *Phyllanthus emblica*: A comprehensive review of its therapeutic benefits. *South African Journal of Botany, 138*, 278-310.

Akihisa, T., Noto, T., Takahashi, A., Fujita, Y., Banno, N., Tokuda, H., Koike, K., Suzuki, T., Yasukawa, K., *et al.* (2009). Melanogenesis inhibitory, anti-inflammatory, and chemopreventive effects of limonoids from the seeds of *Azadirachta indicia* A. Juss.(neem). *Journal of Oleo Science, 58*(11), 581-594.

Akihisa, T., Takahashi, A., Kikuchi, T., Takagi, M., Watanabe, K., Fukatsu, M., Fujita, Y., Banno, N., Tokuda, H., *et al.* (2011). The melanogenesis-inhibitory, anti-inflammatory, and chemopreventive effects of limonoids in *n*-hexane extract of *Azadirachta indica* A. Juss.(neem) seeds. *Journal of Oleo Science, 60*(2), 53-59.

Ali, H., & Dixit, S. (2013). Extraction optimization of *Tinospora cordifolia* and assessment of the anticancer activity of its alkaloid palmatine. *The Scientific World Journal, 2013*, 376216.

Ali, H., Dixit, S., Ali, D., Alqahtani, S. M., Alkahtani, S., & Alarifi, S. (2015). Isolation and evaluation of anticancer efficacy of stigmasterol in a mouse model of DMBA-induced skin carcinoma. *Drug Design, Development and Therapy, 9*, 2793.

Alzohairy, M. A. (2016). Therapeutics role of *Azadirachta indica* (Neem) and their active constituents in diseases prevention and treatment. *Evidence-Based Complementary and Alternative Medicine, 2016*, 7382506.

Anquez-Traxler, C. (2011). The legal and regulatory framework of herbal medicinal products in the European Union: a focus on the traditional herbal medicines category. *Drug Information Journal, 45*(1), 15-23.

Apalla, Z., Nashan, D., Weller, R. B., & Castellsagué, X. (2017). Skin cancer: epidemiology, disease burden, pathophysiology, diagnosis, and therapeutic approaches. *Dermatology and Therapy, 7*(1), 5-19.

Arasada, B. L., Bommareddy, A., Zhang, X., Bremmon, K., & Dwivedi, C. (2008). Effects of α-santalol on proapoptotic caspases and p53 expression in UVB irradiated mouse skin. *Anticancer Research, 28*(1A), 129-132.

Arora, N., Bansal, M., & Koul, A. (2011a). *Azadirachta indica* exerts chemopreventive action against murine skin cancer: studies on histopathological, ultrastructural changes and modulation of NF-κB, AP-1, and STAT1. *Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics, 19*(5), 179-191.

Arora, N., Bansal, M., & Koul, A. (2013). *Azadirachta indica* acts as a pro-oxidant and modulates cell cycle associated proteins during DMBA/TPA induced skin carcinogenesis in mice. *Cell Biochemistry and Function, 31*(5), 385-394.

Arora, N., & Koul, A. (2014). A 'complex solution'to a 'complex'problem. *European Journal of Cancer Prevention, 23*(6), 568-578.

Arora, N., Koul, A., & Bansal, M. (2011b). Chemopreventive activity of *Azadirachta indica* on two-stage skin carcinogenesis in murine model. *Phytotherapy Research, 25*(3), 408-416.

Birt, D. F., Mitchell, D., Gold, B., Pour, P., & Pinch, H. C. (1997). Inhibition of ultraviolet light induced skin carcinogenesis in SKH-1 mice by apigenin, a plant flavonoid. *Anticancer Research, 17*(1A), 85-91.

Boeckmann, L., Martens, M. C., & Emmert, S. (2020). Molecular biology of basal and squamous cell carcinomas. *Sunlight, Vitamin D and Skin Cancer, 1268*, 171-191.

Bommareddy, A., Brozena, S., Steigerwalt, J., Landis, T., Hughes, S., Mabry, E., Knopp, A., VanWert, A. L., & Dwivedi, C. (2019). Medicinal properties of alpha-santalol, a naturally occurring constituent of sandalwood oil. *Natural Product Research, 33*(4), 527-543.

Bommareddy, A., Hora, J., Cornish, B., & Dwivedi, C. (2007). Chemoprevention by α-santalol on UVB radiation-induced skin tumor development in mice. *Anticancer Research, 27*(4B), 2185-2188.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians, 68*(6), 394-424.

Byun, S., Lee, K. W., Jung, S. K., Lee, E. J., Hwang, M. K., Lim, S. H., Bode, A. M., Lee, H. J., & Dong, Z. (2010). Luteolin inhibits protein kinase Cε and c-Src activities and UVB-induced skin cancer. *Cancer Research, 70*(6), 2415-2423.

Chaiprasongsuk, A., & Panich, U. (2022). Role of Phytochemicals in Skin Photoprotection via Regulation of Nrf2. *Frontiers in Pharmacology, 13*, 823881.

Chaudhary, R., Jahan, S., & Goyal, P. K. (2008). Chemopreventive potential of an Indian medicinal plant (*Tinospora cordifolia*) on skin carcinogenesis in mice. *Journal of Environmental Pathology, Toxicology and Oncology, 27*(3), 233-243.

Chilampalli, C., Zhang, X., Kaushik, R. S., Young, A., Zeman, D., Hildreth, M. B., Fahmy, H., & Dwivedi, C. (2013). Chemopreventive effects of combination of honokiol and magnolol with α-santalol on skin cancer developments. *Drug Discoveries & Therapeutics, 7*(3), 109-115.

Chugh, N., & Koul, A. (2021). Altered presence of extra cellular matrix components in murine skin cancer: Modulation by *Azadirachta indica* leaf extract. *Journal of Traditional and Complementary Medicine, 11*(3), 197-208.

Chugh, N. A., Bansal, M. P., & Koul, A. (2018). The effect of *Azadirachta indica* leaf extract on early stages of chemically induced skin cancer in mice. *Journal of Herbs, Spices & Medicinal Plants, 24*(3), 257-271.

Cives, M., Mannavola, F., Lospalluti, L., Sergi, M. C., Cazzato, G., Filoni, E., Cavallo, F., Giudice, G., Stucci, L. S., *et al.* (2020). Non-melanoma skin cancers: Biological and clinical features. *International Journal of Molecular Sciences, 21*(15), 5394.

Dasgupta, T., Banerjee, S., Yadava, P., & Rao, A. (2004a). Chemopreventive potential of *Azadirachta indica* (Neem) leaf extract in murine carcinogenesis model systems. *Journal of Ethnopharmacology, 92*(1), 23-36.

Dasgupta, T., Rao, A., & Yadava, P. (2004b). Chemomodulatory efficacy of basil leaf (*Ocimum basilicum*) on drug metabolizing and antioxidant enzymes, and on carcinogen-induced skin and forestomach papillomagenesis. *Phytomedicine, 11*(2-3), 139-151.

Davis, L., & Kuttan, G. (2001). Effect of *Withania somnifera* on DMBA induced carcinogenesis. *Journal of Ethnopharmacology, 75*(2-3), 165-168.

Deng, G., & Cassileth, B. (2013). Complementary or alternative medicine in cancer care—myths and realities. *Nature Reviews Clinical Oncology, 10*(11), 656-664.

Dickinson, S. E., Olson, E. R., Levenson, C., Janda, J., Rusche, J. J., Alberts, D. S., & Bowden, G. T. (2014). A novel chemopreventive mechanism for a traditional medicine: East Indian sandalwood oil induces autophagy and cell death in proliferating keratinocytes. *Archives of Biochemistry and Biophysics, 558*, 143-152.

Didona, D., Paolino, G., Bottoni, U., & Cantisani, C. (2018). Non melanoma skin cancer pathogenesis overview. *Biomedicines, 6*(1), 6.

Dwivedi, C., & Abu-Ghazaleh, A. (1997). Chemopreventive effects of sandalwood oil on skin papillomas in mice. *European Journal of Cancer Prevention, 6*(4), 399-401.

Dwivedi, C., Guan, X., Harmsen, W. L., Voss, A. L., Goetz-Parten, D. E., Koopman, E. M., Johnson, K. M., Valluri, H. B., & Matthees, D. P. (2003). Chemopreventive effects of α-santalol on skin tumor development in CD-1 and SENCAR mice. *Cancer Epidemiology Biomarkers & Prevention, 12*(2), 151-156.

Dwivedi, C., Valluri, H. B., Guan, X., & Agarwal, R. (2006). Chemopreventive effects of α-santalol on ultraviolet B radiation-induced skin tumor development in SKH-1 hairless mice. *Carcinogenesis, 27*(9), 1917-1922.

Dwivedi, C., & Zhang, Y. (1999). Sandalwood oil prevents skin tumour development in CD1 mice. *European Journal of Cancer Prevention, 8*(5), 449-455.

F'guyer, S., Afaq, F., & Mukhtar, H. (2003). Photochemoprevention of skin cancer by botanical agents. *Photodermatology, Photoimmunology & Photomedicine, 19*(2), 56-72.

Fitzmaurice, C., Allen, C., Barber, R. M., Barregard, L., Bhutta, Z. A., Brenner, H., Dicker, D. J., Chimed-Orchir, O., Dandona, R., *et al.* (2017). Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. *JAMA Oncology, 3*(4), 524-548.

Fujii, T., Okuda, T., Yasui, N., Wakaizumi, M., Ikami, T., & Ikeda, K. (2013). Effects of amla extract and collagen peptide on UVB-induced photoaging in hairless mice. *Journal of Functional Foods, 5*(1), 451-459.

Fujii, T., Wakaizumi, M., Ikami, T., & Saito, M. (2008). Amla (*Emblica officinalis* Gaertn.) extract promotes procollagen production and inhibits matrix metalloproteinase-1 in human skin fibroblasts. *Journal of Ethnopharmacology, 119*(1), 53-57.

Gan, C., Zi, C., Sheng, J., Wang, X., & Xu, H. (2021). Recent Advances on Anti-skin Cancer Activity of Phytochemicals and Underlying Molecular Mechanisms. *Medicine Research, 5*(2), 210006.

George, B., Chandran, R., & Abrahamse, H. (2021). Role of Phytochemicals in Cancer Chemoprevention: Insights. *Antioxidants (Basel), 10*(9), 1455.

Gordon, L. G., Elliott, T. M., Olsen, C. M., Pandeya, N., & Whiteman, D. C. (2018). Multiplicity of skin cancers in Queensland and their cost burden to government and patients. *Australian and New Zealand Journal of Public Health, 42*(1), 86-91.

Goswami, N. B., & Tah, J. (2018). White sandal (*Santalum album* L.), a precious medicinal and timber yielding plant: a short review. *Plant Archives, 18*(1), 1048-1056.

Goyal, P., Chaudhary, R., Jahan, S., & Gupta, U. (2007). Chemo preventive efficacy of tinospora cordifolia (a medicinal plant) against chemical induced skin papillomagenesis in mice. *Cancer Epidemiology Biomarkers & Prevention, 16*(12_Supplement), B5-B5.

Guldiken, B., Ozkan, G., Catalkaya, G., Ceylan, F. D., Yalcinkaya, I. E., & Capanoglu, E. (2018). Phytochemicals of herbs and spices: Health versus toxicological effects. *Food and Chemical Toxicology, 119*, 37-49.

Gupta, A. K., Bharadwaj, M., & Mehrotra, R. (2016). Skin cancer concerns in people of color: risk factors and prevention. *Asian Pacific Journal of Cancer Prevention, 17*(12), 5257-5264.

Hussain, S. A., Panjagari, N. R., Singh, R., & Patil, G. (2015). Potential herbs and herbal nutraceuticals: food applications and their interactions with food components. *Critical Reviews in Food Science and Nutrition, 55*(1), 94-122.

Ijaz, S., Akhtar, N., Khan, M. S., Hameed, A., Irfan, M., Arshad, M. A., Ali, S., & Asrar, M. (2018). Plant derived anticancer agents: A green approach towards skin cancers. *Biomedicine & Pharmacotherapy, 103*, 1643-1651.

Kan, Z., Jaiswal, B. S., Stinson, J., Janakiraman, V., Bhatt, D., Stern, H. M., Yue, P., Haverty, P. M., Bourgon, R., *et al.* (2010). Diverse somatic mutation patterns and pathway alterations in human cancers. *Nature, 466*(7308), 869-873.

Katalinic, A., Kunze, U., & Schäfer, T. (2003). Epidemiology of cutaneous melanoma and non-melanoma skin cancer in Schleswig-Holstein, Germany: incidence, clinical subtypes, tumour stages and localization (epidemiology of skin cancer). *British Journal of Dermatology, 149*(6), 1200-1206.

Katta, R., & Brown, D. N. (2015). Diet and skin cancer: The potential role of dietary antioxidants in nonmelanoma skin cancer prevention. *Journal of Skin Cancer, 2015*, 893149.

Kaur, G., Athar, M., & Alam, M. S. (2010). Eugenol precludes cutaneous chemical carcinogenesis in mouse by preventing oxidative stress and inflammation and by inducing apoptosis. *Molecular Carcinogenesis: Published in Cooperation with the University of Texas MD Anderson Cancer Center, 49*(3), 290-301.

Kaur, M., Agarwal, C., Singh, R. P., Guan, X., Dwivedi, C., & Agarwal, R. (2005). Skin cancer chemopreventive agent, α-santalol, induces apoptotic death of human epidermoid carcinoma A431 cells via caspase activation together with dissipation of mitochondrial membrane potential and cytochrome c release. *Carcinogenesis, 26*(2), 369-380.

Khan, A., Ahmad, A., Akhtar, F., Yousuf, S., Xess, I., Khan, L. A., & Manzoor, N. (2010). *Ocimum sanctum* essential oil and its active principles exert their antifungal activity by disrupting ergosterol biosynthesis and membrane integrity. *Research in Microbiology, 161*(10), 816-823.

Khan, S., Ikram, M., & Faisal, M. (2021). Commercial, Cosmetic, and Medicinal Importance of Sandal (*Santalum album*): A Valuable Forest Resource. In *Non-Timber Forest Products* (pp. 129-144): Springer.

Koh, D., Wang, H., Lee, J., Chia, K., Lee, H., & Goh, C. (2003). Basal cell carcinoma, squamous cell carcinoma and melanoma of the skin: analysis of the Singapore Cancer Registry data 1968–97. *British Journal of Dermatology, 148*(6), 1161-1166.

Koul, A., Ghara, A. R., & Gangar, S. C. (2006). Chemomodulatory effects of *Azadirachta indica* on the hepatic status of skin tumor bearing mice. *Phytotherapy Research, 20*(3), 169-177.

Kumar, A. A., Joshi, G., & Ram, H. M. (2012). Sandalwood: history, uses, present status and the future. *Current Science, 103*(12), 1408-1416.

Labani, S., Asthana, S., Rathore, K., & Sardana, K. (2021). Incidence of melanoma and nonmelanoma skin cancers in Indian and the global regions. *Journal of Cancer Research and Therapeutics, 17*(4), 906-911.

Lauth, M., Unden, A. B., & Toftgård, R. (2004). Non-melanoma skin cancer: pathogenesis and mechanisms. *Drug Discovery Today: Disease Mechanisms, 1*(2), 267-272.

Lee, D. A., & Miller, S. J. (2009). Nonmelanoma skin cancer. *Facial Plastic Surgery Clinics of North America, 17*(3), 309-324.

Leiter, U., Keim, U., Eigentler, T., Katalinic, A., Holleczek, B., Martus, P., & Garbe, C. (2017). Incidence, mortality, and trends of nonmelanoma skin cancer in Germany. *Journal of Investigative Dermatology, 137*(9), 1860-1867.

Lengai, G. M., Muthomi, J. W., & Mbega, E. R. (2020). Phytochemical activity and role of botanical pesticides in pest management for sustainable agricultural crop production. *Scientific African, 7*, e00239.

Li, W., Zhang, C., Du, H., Huang, V., Sun, B., Harris, J. P., Richardson, Q., Shen, X., Jin, R., *et al.* (2016). Withaferin A suppresses the up-regulation of acetyl-coA carboxylase 1 and skin tumor formation in a skin carcinogenesis mouse model. *Molecular Carcinogenesis, 55*(11), 1739-1746.

Li, W., & Zhao, Y. (2013). Withaferin A suppresses tumor promoter 12-*O*-tetradecanoylphorbol 13-acetate-induced decreases in isocitrate dehydrogenase 1 activity and mitochondrial function in skin epidermal JB 6 cells. *Cancer Science, 104*(2), 143-148.

Majeed, M., Bhat, B., Anand, S., Sivakumar, A., Paliwal, P., & Geetha, K. (2011). Inhibition of UV-induced ROS and collagen damage by *Phyllanthus emblica* extract in normal human dermal fibroblasts. *Journal of Cosmetic Science, 62*(1), 49-56.

Maliyakkal, N., Appadath Beeran, A., Balaji, S. A., Udupa, N., Ranganath Pai, S., & Rangarajan, A. (2015). Effects of *Withania somnifera* and *Tinospora cordifolia* extracts on the side population phenotype of human epithelial cancer cells: toward targeting multidrug resistance in cancer. *Integrative Cancer Therapies, 14*(2), 156-171.

Mandal, A. K., Poudel, M., Neupane, N. P., & Verma, A. (2022). Phytochemistry, Pharmacology, and Applications of Ocimum sanctum (Tulsi): Springer Link.

Mandlik, D. S., & Namdeo, A. G. (2021). Immunomodulators and Phytodrugs. In *Evidence Based Validation of Traditional Medicines* (pp. 901-920): Springer.

Marwat, S. K., Khan, M. S., Ghulam, S., Anwar, N., Mustafa, G., & Usman, K. (2011). Phytochemical constituents and pharmacological activities of sweet Basil-*Ocimum basilicum* L.(Lamiaceae). *Asian Journal of Chemistry, 23*(9), 3773.

Mathur, S., Kaur, P., Sharma, M., Katyal, A., Singh, B., Tiwari, M., & Chandra, R. (2004). The treatment of skin carcinoma, induced by UV B radiation, using 1-*oxo*-5β, 6β-epoxy-witha-2-enolide, isolated from the roots of *Withania somnifera*, in a rat model. *Phytomedicine, 11*(5), 452-460.

Mehmood, M. H., Siddiqi, H. S., & Gilani, A. H. (2011). The antidiarrheal and spasmolytic activities of *Phyllanthus emblica* are mediated through dual blockade of muscarinic receptors and Ca^{2+} channels. *Journal of Ethnopharmacology, 133*(2), 856-865.

Millsop, J. W., Sivamani, R. K., & Fazel, N. (2013). Botanical agents for the treatment of nonmelanoma skin cancer. *Dermatology Research and Practice, 2013*, 837152.

Naja, F., Fadel, R. A., Alameddine, M., Aridi, Y., Zarif, A., Hariri, D., Mugharbel, A., Khalil, M., Nahleh, Z., *et al.* (2015). Complementary and alternative medicine use and its association with quality of life among Lebanese breast cancer patients: a cross-sectional study. *BMC Complementary and Alternative Medicine, 15*(1), 1-10.

Nayak, B., & Pinto Pereira, L. M. (2006). *Catharanthus roseus* flower extract has wound-healing activity in Sprague Dawley rats. *BMC Complementary and Alternative Medicine, 6*(1), 1-6.

Padmavathi, B., Rath, P. C., Rao, A. R., & Singh, R. P. (2005). Roots of *Withania somnifera* inhibit forestomach and skin carcinogenesis in mice. *Evidence-Based Complementary and Alternative Medicine, 2*(1), 99-105.

Pham, H. N. T., Sakoff, J. A., Van Vuong, Q., Bowyer, M. C., & Scarlett, C. J. (2018). Screening phytochemical content, antioxidant, antimicrobial and cytotoxic activities of *Catharanthus roseus* (L.) G. Don stem extract and its fractions. *Biocatalysis and Agricultural Biotechnology, 16*, 405-411.

Pham, H. N. T., Sakoff, J. A., Vuong, Q. V., Bowyer, M. C., & Scarlett, C. J. (2019). Phytochemical, antioxidant, anti-proliferative and antimicrobial properties of *Catharanthus roseus* root extract, saponin-enriched and aqueous fractions. *Molecular Biology Reports, 46*(3), 3265-3273.

Prakash, J., Gupta, S. K., & Dinda, A. K. (2002). *Withania somnifera* root extract prevents DMBA-induced squamous cell carcinoma of skin in Swiss albino mice. *Nutrition and Cancer, 42*(1), 91-97.

Prashar, R., & Kumar, A. (1995). Chemopreventive action of *Ocimum sanctum* on 2, 12-dimethylbenz (a) anthracene DMBA-induced papillomagenesis in the skin of mice. *International Journal of Pharmacognosy, 33*(3), 181-187.

Prashar, R., Kumar, A., Banerjee, S., & Rao, A. (1994). Chemopreventive action by an extract from *Ocimum sanctum* on mouse skin papillomagenesis and its enhancement of skin glutathione S-transferase activity and acid soluble sulfydryl level. *Anti-Cancer Drugs, 5*(5), 567-572.

Queen, L. (2017). *Skin cancer: causes, prevention, and treatment.* (Senior Honors Theses). Liberty University, (648).

Rastogi, S., Shukla, Y., Paul, B. N., Chowdhuri, D. K., Khanna, S. K., & Das, M. (2007). Protective effect of *Ocimum sanctum* on 3-methylcholanthrene, 7, 12-dimethylbenz (a) anthracene and aflatoxin B1 induced skin tumorigenesis in mice. *Toxicology and Applied Pharmacology, 224*(3), 228-240.

Rees, J. R., Zens, M. S., Gui, J., Celaya, M. O., Riddle, B. L., & Karagas, M. R. (2014). Non melanoma skin cancer and subsequent cancer risk. *PloS One, 9*(6), e99674.

Rezadoost, M. H., Kumleh, H. H., & Ghasempour, A. (2019). Cytotoxicity and apoptosis induction in breast cancer, skin cancer and glioblastoma cells by plant extracts. *Molecular Biology Reports, 46*(5), 5131-5142.

Sancheti, G., Jindal, A., Kumari, R., & Goyal, P. (2005). Chemopreventive action of *Emblica officinalis* on skin carcinogenesis in mice. *Asian Pacific Journal of Cancer Prevention, 6*(2), 197-201.

Santha, S., & Dwivedi, C. (2015). Anticancer effects of sandalwood (*Santalum album*). *Anticancer Research, 35*(6), 3137-3145.

Seite, S., Del Marmol, V., Moyal, D., & Friedman, A. (2017). Public primary and secondary skin cancer prevention, perceptions and knowledge: an international cross-sectional survey. *Journal of the European Academy of Dermatology and Venereology, 31*(5), 815-820.

Singh, E., Sharma, S., Pareek, A., Dwivedi, J., Yadav, S., & Sharma, S. (2012). Phytochemistry, traditional uses and cancer chemopreventive activity of Amla (*Phyllanthus emblica*): The Sustainer. *Journal of Applied Pharmaceutical Science, 2*(1), 176-183.

Sloan, F. A., & Gelband, H. (2007). Defining resource-level-appropriate cancer control. In *Cancer Control Opportunities in Low-and Middle-Income Countries*: National Academies Press (US).

Sobanko, J. F., Sarwer, D. B., Zvargulis, Z., & Miller, C. J. (2015). Importance of physical appearance in patients with skin cancer. *Dermatologic Surgery, 41*(2), 183-188.

Stoj, V., Shahriari, N., Shao, K., & Feng, H. (2022). Nutrition and nonmelanoma skin cancers. *Clinics in Dermatology, 40*(2), 173-185.

Sukumaran, K., Unnikrishnan, M., & Kuttan, R. (1994). Inhibition of tumour promotion in mice by eugenol. *Indian Journal of Physiology and Pharmacology, 38*(4), 306-308.

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians, 71*(3), 209-249.

Thomasset, S. C., Berry, D. P., Garcea, G., Marczylo, T., Steward, W. P., & Gescher, A. J. (2007). Dietary polyphenolic phytochemicals—promising cancer chemopreventive agents in humans? A review of their clinical properties. *International Journal of Cancer, 120*(3), 451-458.

Treichel, T. L. E., do Prado, T. D., do Amaral, A. S. Z., de Sousa Gomes, Y., da Rocha Pinto, L., Martins, G. T., Martins, A. T., & Cagnini, D. Q. (2020). Use of Ointment or Aqueous Extract of Neem (*Azadirachta indica*) for the Repair of Experimental Skin Lesions in Sheep. *American Journal of Plant Sciences, 11*(5), 100290.

Upadhyay, A. K., Kumar, K., Kumar, A., & Mishra, H. S. (2010). *Tinospora cordifolia* (Willd.) Hook. f. and Thoms.(Guduchi)–validation of the Ayurvedic pharmacology through experimental and clinical studies. *International Journal of Ayurveda Research, 1*(2), 112-121.

Van Dross, R. T., Hong, X., Essengue, S., Fischer, S. M., & Pelling, J. C. (2007). Modulation of UVB-induced and basal cyclooxygenase-2 (COX-2) expression by apigenin in mouse keratinocytes: Role of USF transcription factors. *Molecular Carcinogenesis: Published in Cooperation with the University of Texas MD Anderson Cancer Center, 46*(4), 303-314.

Wei, H., Tye, L., Bresnick, E., & Birt, D. F. (1990). Inhibitory effect of apigenin, a plant flavonoid, on epidermal ornithine decarboxylase and skin tumor promotion in mice. *Cancer Research, 50*(3), 499-502.

Wollina, U., Koch, A., Schönlebe, J., & Tchernev, G. (2017). Carcinosarcoma of skin (sarcomatoid carcinoma)-A rare non-melanoma slin cancer (Case Review). *Georgian Medical News, 263*, 7-10.

Wölfle, U., Esser, P. R., Simon-Haarhaus, B., Martin, S. F., Lademann, J., & Schempp, C. M. (2011). UVB-induced DNA damage, generation of reactive oxygen species, and inflammation are effectively attenuated by the flavonoid luteolin in vitro and in vivo. *Free Radical Biology and Medicine, 50*(9), 1081-1093.

Wu, X., Elkin, E. E., & Marghoob, A. A. (2015). Burden of basal cell carcinoma in USA. *Future Oncology, 11*(22), 2967-2974.

Xu, K., Zhang, C., Li, Y., Xi, X., Zheng, L., Meng, M., Liu, T., Zhao, Y., & Li, W. (2019). Withaferin A suppresses skin tumor promotion by inhibiting proteasome-dependent isocitrate dehydrogenase 1 degradation. *Translational Cancer Research, 8*(6), 2449.

Yates, C. R., Bruno, E. J., & Yates, M. E. (2022). *Tinospora cordifolia*: A review of its immunomodulatory properties. *Journal of Dietary Supplements, 19*(2), 271-285.

Zhang, X., Chen, W., Guillermo, R., Chandrasekher, G., Kaushik, R. S., Young, A., Fahmy, H., & Dwivedi, C. (2010). Alpha-santalol, a chemopreventive agent against skin cancer, causes G2/M cell cycle arrest in both p53-mutated human epidermoid carcinoma A431 cells and p53 wild-type human melanoma UACC-62 cells. *BMC Research Notes, 3*(1), 1-15.