

Integrative Bioinformatics Approach to Identify Skin Cancer Associated Genes and Evaluate Phytochemical from Indian Medicinal Plants



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Integrative Bioinformatics Approach to Identify Skin Cancer Associated Genes and Evaluate Phytochemical from Indian Medicinal Plants

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Abstract

The aggressive nature of melanoma makes skin cancer an enormous global health and economic concern, as evidenced by rising incidence and mortality rates. According to current statistics, there are more than 1.5 million new cases of skin cancers worldwide yearly, including squamous and basal cell carcinomas, which are less deadly even though being more common. The fundamental cause is abnormal skin cell proliferation brought on by genetic abnormalities or DNA mutations. Important genes linked to the pathophysiology of skin cancer, notably CDK4 and BRAF, have been found using integrative bioinformatics techniques. At the same time, phytochemicals derived from Indian medicinal plants have become well-known for their ability to treat and prevent skin cancer.

Keywords: Cancer, Melanoma, Leptin, Epidermis, Allium

1. Introduction

Skin cancer is a global public health concern, and its burden is always increasing, which may have major repercussions on both the global economy and manpower [1].

According to the International Agency for Research on Cancer's annual status report, there were roughly 9.6 million cancer-related deaths and 18.1 million new cancer cases worldwide in 2018. Skin malignancies are the most prevalent type of cancer diagnosed globally, with over 1.5 million new cases expected in 2022. In 2022, an estimated 330000 new instances of melanoma were discovered worldwide, with nearly 60000 people dying from the condition. Melanoma incidence rates vary greatly by country and world region. Melanoma affects more men than women in the majority of the world's countries.

According to the American Cancer Society's figures, the number of new cases of melanoma among all malignancies is expected to be 6% in men and 4% in women by 2023. Skin malignancies (the majority of which are basal and squamous cell carcinomas) are the most frequent type of cancer in the United States. According to one estimate, 5.4 million basal and squamous cell skin malignancies are diagnosed in the United States each year (affecting around 3.3 million people, as some have several). Approximately eight out of ten of these are basal cell tumors. Squamous cell cancer occurs less frequently. Although basal and squamous cell skin malignancies are frequent, they are rarely fatal. In the United States, estimates range from 2,000 to 8,000 people each year (primarily due to squamous cell skin cancer).

The prevalence of these tumors has been rising for many years. This is most likely due to improvements in skin cancer detection, increased sun exposure, and longer life expectancy.

The etiology is mostly based on aberrant skin cell proliferation facilitated by unrepaired DNA caused by DNA mutations or genetic abnormalities [2]. The skin's tissue is separated into two layers: the top epidermis, which is made up of epithelial cells and pigmented melanocytes, and the bottom dermis, which is a layer of connective tissue that holds blood vessels, hair follicles, and sweat glands.

Skin cancer begins with the development of cells on the skin. The cells are capable of invading and destroying healthy biological tissue. Sometimes the cells separate and spread to other places of the body [3]. There are many different types of skin cancer. The two most frequent types of skin cancer are basal cell carcinoma and squamous cell carcinoma. While they are the most prevalent, they are usually curable. Melanoma is the most serious kind of skin cancer. It has a higher spread rate, making it more difficult to treat [4]

Traditional medicine has been performed around the world since ancient times, utilizing natural bioactive components. Natural dietary phytochemicals have received a lot of attention in this field due to their diverse therapeutic advantages in reversing disease development. These bioactive phytochemicals, found in a variety of foods and beverages, are less harmful and more effective as medications [5]. They can be integrated into the host's natural defence against parasites, viruses, and other external stimuli. In specific situations, phytochemicals may be extremely beneficial in the treatment of skin cancer.

The purpose of this review article is to investigate the impact of an integrative bioinformatics method in identifying genes related with skin cancer, specifically CDK4 and BRAF, and to assess the chemo preventive and therapeutic potential of phytochemicals derived from Indian medicinal plants. The publication also discusses the molecular insights, antioxidant, antibacterial, and photoprotective effects that these phytochemicals have in the fight against skin cancer.

2. Skin: Outermost Protective Layer

The skin is the human body's outermost and biggest organ. It acts as a barrier, protecting the body from UV rays and other dangerous substances while also regulating the body's temperature.

There are three layers of skin: the epidermis, which is the outermost layer, the dermis, which is beneath the epidermis, and the hypodermis.

The epidermis is made up of three cell systems: keratinocytes and Langerhans cells in the Malpighian layer, and melanocytes in the basal layer. Keratinocyte cells generate keratin, a thread-like protein that has an important protective role. The thickness of the layer varies according to the area of the body [6].

The dermis is the middle layer underneath the epidermis and is composed of collagen protein with a fibril structure. The subcutaneous tissue has a dermis layer made up of lipocytes, which are little fat cell projections. The dermis consists of three distinct cells: mast cells, macrophages, and fibroblasts.

The hypodermis, often known as subcutaneous tissue, lies beneath the dermis. Its attachment to the skin serves to support muscle and bone while also providing blood and nerve supply. This layer is composed of elastin and loose connective tissue. They are made up of diverse cells, including adipocytes, fibroblasts, and macrophages. The hypodermis layer is made up of around 50% fat, which serves as the body's protection and insulation. Lipocytes generate a hormone called leptin, which regulates body weight [7].

3. Grades of Skin Cancer

The World Health Organization (WHO) grades skin cancer from I to IV. Table 1 shows some of the basic characteristics of these malignancies.

Table 1: Main characteristics of Skin Cancer (Grade I to IV)

GRADE	CHARACTERISTICS
I	They mostly appear like normal cells/tissues and are considered low-graded tumors and well-differentiated.
II	These tumors have a slightly abnormal appearance and are known as moderately differentiated.
III	These tissues appear extremely aberrant and poorly differentiated. Grade three is considered a high grade.
IV	They appear more aberrant than other cells and tissues. They have higher grades and spread more quickly than other lesser grades.

4. Types of skin cancer

Skin cancer is caused by abnormal skin cell proliferation and most commonly arises on sun-exposed skin. The sun's UV rays, as well as tanning beds, have been linked to a variety of skin cancers. Family history and genetics may also play a role. Mutated cells can rapidly proliferate and reproduce, resulting in both malignant and benign tumors. Skin cancer is frequently identified in a pre-cancerous stage—before it penetrates beyond the skin's surface or progresses to a more advanced stage.

4.1. Basal cell carcinoma

Basal cell carcinoma is the most common type of skin cancer, accounting for 80% of occurrences. Basal cell carcinomas typically develop on the sun-exposed skin of the face, head, and neck. They grow slowly and rarely spread to other areas of the body. It is thought that BCC developed from trichoblasts, which are follicle-sebaceous-apocrine germs [8]

4.2. Squamous cell carcinoma

Squamous cell carcinomas squamous cell carcinoma, also known as cutaneous cell carcinoma, accounts for around 20% of NMSC. Squamous cells are flat epidermal cells that regenerate and shed from the skin's outer layers. Squamous cell carcinomas typically appear on sun-exposed areas such as the face, ears, neck, lips, and backs of the hands. They can also form scars or chronic skin sores. Bowen's illness is a precancerous or in situ kind of SCC that affects only the skin's peripheral layer. They are generated from the flat squamous cells that make up the majority of the epidermis, the peripheral layer of the skin.

4.3. Melanoma

Every year, this deadly skin disease kills 9,000 people in the United States. Melanoma is also known as malignant melanoma. This type of cancer begins in the melanocytes, which are cells that produce the dark pigment melanin. Around 25% of melanoma cases originate from moles. Melanoma is indicated by changes in the mole's size, color, uneven margins, and itching. Melanoma is caused by decreased pigment levels and UV light exposure. Melanin is the body's natural sunscreen, shielding the deeper layers of skin from the damaging effects of the sun. Melanoma is less frequent than other types of skin cancer, but if not treated early, it has a higher risk of spreading to other parts of the body [9]

5. Role of CDK4 and BRAF genes in Skin Cancer

In melanoma, both CDK4 and BRAF genes play important roles in tumor formation and progression

5.1. CDK4 gene

CDK4 is a gene that encodes a protein in the serine/threonine kinase family. The protein promotes cell cycle progression from G1 to S phase and activates RB1. Endometrial cancer, intestinal cancer, and skin cancer all have missense and silent mutations. Mutations in CDK4 can disrupt the cell cycle, resulting in uncontrolled cell proliferation and the formation of melanoma. The CDK4 gene, which encodes a cyclin-dependent kinase, is linked to skin cancer, particularly melanoma [10]. Cyclin-dependent kinases (CDKs) drive cell cycle progression, modulate transcriptional activity, and hence control cell proliferation. Cancer is characterized by aberrant cell cycle entry and uncontrolled cell proliferation.

5.2. BRAF gene

Melanoma, a serious type of skin cancer, is frequently associated with mutations of the BRAF gene. Mutations in BRAF can cause uncontrolled cell proliferation, which contributes to tumor formation. Approximately half of all melanomas contain a BRAF mutation, most often the BRAF V600E mutation. These mutations can cause the melanoma to grow more aggressively and can be targeted with certain medicines [11]. The BRAF gene, located on chromosome 7 (7q34), encodes the BRAF protein, a 94-kDa intracellular enzyme with 766 amino acids implicated in the mitogen activated protein kinase (MAPK) pathway. The MAPK pathway is a sequence of intracellular proteins that regulate physiological cell processes like growth, differentiation, proliferation, and death [12]

6. Indian Medicinal Plants and Their Therapeutic Potential in Skin Cancer

Traditional Indian medicine systems such as Ayurveda, Siddha, and Unani include a huge library of medicinal plants used to treat skin diseases. India's rich heritage of traditional medicine provides a valuable supply of natural substances with anti-cancer properties. The bioactive phytochemicals found in these plants have antioxidant, anti-inflammatory, antiproliferative, and photoprotective characteristics, making them interesting candidates for skin cancer prevention and treatment

6.1. Indian Medicinal Plants with Anti-Skin Cancer Properties

Table 2: Medicinal effects in Skin Cancer

Indian Plants	Active compound	Mechanisms	Effects in Skin Cancer
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<i>Curcuma longa</i>	Curcumin	Antioxidant, Anti-inflammatory apoptosis induction	Reduces tumor progression
<i>Azadirachta indica</i>	Nimbolide, Nimbin	Oxidative stress mediated apoptosis inhibition of EMT	Suppresses tumor progression
<i>Withania somnifera</i>	Withaferin A	Antioxidant activity, DNA Protection	Inhibits metastasis
<i>Phyllanthus emblica</i>	Gallic acid, Vitamin C	Anti-inflammatory ROS Quenching	Prevents UV-induced damage
<i>Ocimum sanctum</i>	Eugenol, Ursolic acid	Anti-inflammatory ROS Quenching	Protects against carcinogenesis

6.2. Mechanistic Insight

- Antioxidant Shield: Neutralizing free radicals to prevent oxidative DNA damage
- Anti-inflammatory Action: Suppressing COX-2 and pro-inflammatory cytokines
- Apoptosis Induction: Modulating intrinsic (mitochondrial) and extrinsic apoptotic pathways
- Photoprotection: Enhancing cellular defence against UVB radiation induction skin damage
- Immune Modulation: Stimulating cytotoxic T cells and natural killer (NK) cell activity

Despite promising preclinical data, the bioavailability, standardization and clinical validation of Indian plant-based therapies for skin cancer remain major hurdles. Indian medicinal plants offer a treasure trove of therapeutic molecules against skin cancer, blending the wisdom of ancient traditions with modern scientific rigor [13]

7. Phytochemicals

Phytochemicals are physiologically active substances obtained from plants and herbal extracts. These drugs appear to be useful in the fight against cancer because they have anti-carcinogenic properties, are widely available, well tolerated, and cost-effective. Evidence suggests that phytochemicals anti-carcinogenic abilities are related to their anti-oxidative, anti-inflammatory, anti-proliferative, and anti-angiogenic effects [14]. Phytochemicals could play a unique role in skin cancer.

Polyphenols, phenolic acids, flavonoids, diarylalkanoids, carotenoids, lignans, anthocyanins, coumarins, terpenes, and sterols are among the over 25,000 phytonutrients identified by studies [15]

7.1. Phenolic compound

Phenolic chemicals, particularly polyphenols, are a type of common compound found in many natural plants and herbs. More than 8000 phenolic structures are currently recognized, and over 4000 flavonoids have been found. Phenolic chemicals are widely dispersed across the plant kingdom and constitute an important class of secondary metabolites in plants. They can be present in many plant tissues, including fruits, nuts, cereals, legumes, and spices. These chemicals serve important roles in a variety of physiological processes, including boosting plant quality, enhancing color and flavour characteristics, and increasing stress resistance. These chemicals can be further classified into numerous classes, with the principal groupings of phenolic compounds being phenolic acids, flavonoids, tannins, stilbenes, coumarins, and lignans [15].

7.2. Flavonoids

Flavonoids are a class of natural substances with varying phenolic structures that can be found in a wide variety of plants, fruits and herbs. These phytochemicals, mostly attributable to their anti-oxidative, anti-inflammatory, and anti-carcinogenic capabilities, are widely known for their therapeutic effects against different disorders, including skin cancer. Flavonoids are a broad category of phenolic chemicals that includes flavones, flavonols, flavanones, flavanols (catechins), anthocyanins, and isoflavones. They are commonly found in fruits, vegetables, grains, and beverages like as tea and wine. Flavonoids in plants provide a variety of functions, including regulating cell growth, attracting pollinating insects, protecting enzymes and vitamins, and giving protection against both biotic and abiotic stresses.

7.3. Tannins

Tannins are a type of phenolic chemical found in plant-based foods such as tea, coffee, cocoa, and fruits like grapes and pomegranates. They add to the astringent flavour in these dishes [16]. Tannins are high-molecular-weight (500-3000 Dalton), heterogeneous, and water-soluble chemicals found in plants and commonly used in food and beverages. Plant-derived tannins are bitter, non-nitrogenous polyphenolic compounds with molecular weights ranging from 20,000 for proanthocyanidins to 500-3000 for gallic acid esters. These are colloidal compounds that may be hydrolysable tannins.

7.4. Alkaloids

The phytochemical class includes a wide range of molecules obtained from plants, animals, microorganisms, and other sources. Alkaloids are among the phytochemicals with the most potential anti-cancer properties. Low molecular weight alkaloids are organic nitrogenous chemicals. Compounds in this category are generally colorless and non-volatile, with a low toxicity to human cells [17]. Alkaloids suppress cancer cells by blocking the topoisomerase enzyme, which further delays DNA replication and increases cell death. Alkaloids are organic molecules that, with rare exceptions, have a basic character and include at least one nitrogen atom, preferably in a heterocycle.

7.5. Terpenoids

Terpenoids, commonly known as terpenes, have been extensively examined and shown to have important roles in human health. Terpenes are phytochemicals that are plentiful and prolific. Terpenes are found in a variety of sources, including plants, flowers, and insects. The chemicals are responsible for the flavor and aroma of plants [18]. Terpenes can be classified according to the amount of isoprene units and their arrangement. They have a variety of biological activities, including anti-cancer, anti-parasitic, anti-microbial, anti-allergenic, anti-spasmodic, anti-hyper-gly-caemic, anti-inflammatory, and immunomodulatory effects.

7.6. Organosulfur

Organosulfur compounds (OSCs) are naturally occurring sulfur-containing phytochemicals primarily found in *Allium* species (e.g., garlic, onions) and cruciferous vegetables (e.g., broccoli, cabbage, Brussels sprouts). These bioactive molecules have been extensively studied for their chemo-preventive, antioxidant, antimicrobial, and anti-carcinogenic properties [19]. In skin cancer, OSCs show promise due to their ability to modulate carcinogen metabolism, enhance detoxification enzymes, suppress inflammation, and regulate cell cycle progression and apoptosis.

7.7. Steroid

Steroidal phytochemicals are a class of bioactive compounds naturally derived from plants that share structural similarity to animal steroids. These compounds, often referred to as plant steroids or phyto-steroids, include steroidal saponins, diosgenin, so lasodine, and stigmasterol. They are known for their ability to interact with steroid hormone receptors and modulate a variety of biological responses relevant to cancer prevention and therapy [20].

Table 3: Summary of phytochemicals compound in skin cancer

Category	Plant name	Phytochemical
Phenolic Compound	Ginger (<i>Zingiber officinale</i>)	Gingerol Zingerone Paradol
	Chilli (<i>Capsicum annuum</i>)	Capsaicin
	Cinnamon (<i>Cinnamomum verum</i>)	Eugenol
	Turmeric (<i>Curcuma longa</i>)	Curcumin
	Coffee (<i>Coffea arabica</i>)	Caffeic acid

Flavonoids	Green tea (<i>Camellia sinensis</i>)	Epigallocatechin gallate
	Soy bean (<i>Glycine max</i>)	Genistein
	Carrot (<i>Daucus cartoa</i>)	Luteolin
	Milk Thistle (<i>Silybium marianum</i>)	Isosilybin A Isosilybin B
	Kaamla Tree (<i>Mallotus philippensis</i>)	Rottlerin
	Lesser galangal (<i>Alpinia officinarum</i>)	Galangin
Alkaloids	Cauliflower (<i>Brassica oleracea</i>)	Indole-3-carbinol
	Dutch eggplant (<i>Solanum aculeatissimum</i>)	Solasonine
	Harmal or wild rue (<i>Peganum Harmala</i>)	Harmine Harmaline
	Indian Barberry (<i>Berberis aristata</i>)	Berberine

Terpenoids	Thyme (<i>Thymus vulgaris</i>)	Ursolic acid
	Black seed (<i>Nigella sativa</i>)	Thymoquinone
	Northern white-cedar (<i>Thuja occidentalis</i>)	Thujone
	Licorice (<i>Glycyrrhiza glabra</i>)	Apioglycyrrhizin
	Roman hyssop (<i>Satureja thymbra</i>)	Linalool
Steroid	Ashwagandha (<i>Withania somnifera</i>)	Withaferin A
Organosulfur	Garlic (<i>Allium sativum</i>)	Diallyl sulfide Diallyl disulfide Diallyl trisulfide
	Mangosteen (<i>Garcinia mangostana</i>)	Xanthone
	Cauliflower (<i>Brassica oleracea</i>)	Sulforaphane

8. Antioxidant activity

Although the skin has a sophisticated antioxidant defense system to combat oxidative stress, excessive and chronic exposure to UV light or other oxidizing agents (e.g., cigarette smoke) can overwhelm the cutaneous antioxidant and immune response capacity, resulting in oxidative damage and immunotoxicity, premature skin aging, and skin cancer. Antioxidant functions have been linked to reduced oxidative stress, DNA damage, malignant transformation, and other cell damage parameters in vitro, as well as a lower incidence of certain forms of cancer and degenerative disorders. Antioxidants reduce the harmful effects of reactive oxygen species (ROS) and can hinder or reverse many of the processes that contribute to epidermal toxicity and disease. The skin has a network of antioxidants to defend itself. Enzymatic antioxidants such as glutathione peroxidase, superoxide dismutase, and catalase, as well as nonenzymatic low-molecular-weight antioxidants like vitamin E isoforms, vitamin C, glutathione (GSH), uric acid, and ubiquinol [21] Several other

components found in skin are powerful antioxidants such as ascorbate, uric acid, carotenoids, and sulfhydryls. Plasma contains water-soluble antioxidants such as glucose, pyruvate, uric acid, ascorbic acid, bilirubin, and glutathione. Lipid-soluble antioxidants consist of alpha-tocopherol, ubiquinol-10, lycopene, β -carotene, lutein, zeaxanthin, and alpha-carotene. In general, the epidermis, the outer layer of the skin, contains larger quantities of antioxidants than the dermis. Oxidative stress is fundamental in the development of skin cancer, as it enhances DNA damage, lipid peroxidation, and protein oxidation. Prolonged exposure to ultraviolet (UV) radiation, particularly UVB, leads to the formation of reactive oxygen species (ROS) like superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($\bullet OH$) within the skin. These ROS can cause mutations in critical tumor suppressor genes such as p53 and trigger oncogenic signaling pathways like NF- κ B and MAPK, facilitating cellular transformation and the progression of tumors. Additionally, oxidative stress intensifies chronic inflammation, supports angiogenesis, and impairs immune response, thereby creating an environment conducive to the onset of skin cancer.

Phytochemicals primarily exert their antioxidant effects by directly scavenging free radicals. Phenolic compounds are particularly effective as they can donate hydrogen atoms or electrons, thus neutralizing reactive oxygen species (ROS) and halting oxidative chain reactions. The DPPH (2,2-diphenyl-1-picrylhydrazyl) assay assesses the capacity of a compound to scavenge free radicals by observing colorimetric changes. The hydrogen peroxide scavenging assay tests how well antioxidants can break down H_2O_2 , a reactive oxygen species that can cross cell membranes and induce oxidative damage. By neutralizing these oxidative species, phytochemicals play a crucial role in preserving cellular integrity and preventing oxidative DNA mutations, which can lead to skin carcinogenesis.

Phytochemicals also enhance the body's innate defense mechanisms by promoting the activity of antioxidant enzymes, such as:

- Superoxide dismutase (SOD), which transforms superoxide radicals into hydrogen peroxide.
- Catalase (CAT), which processes hydrogen peroxide into water and oxygen.
- Glutathione peroxidase (GPx), which converts peroxides into harmless molecules.

An increased expression or activity of these enzymes' aids in alleviating oxidative stress in skin cells, especially in conditions of UV exposure [22].

9. Antimicrobial activity

Recent studies have illuminated the intricate interplay between the skin microbiome and the onset of skin cancer. Dysbiosis, characterized by an imbalance within microbial communities on the skin, can lead to chronic inflammation, immune suppression, and potentially direct DNA damage, all of which are known contributors to carcinogenesis. Specific microbial entities, such as *Staphylococcus aureus* and *Cutibacterium acnes*, have been identified as factors that can elevate oxidative stress and initiate inflammatory responses that may aid tumor development. Furthermore, oncogenic viruses, including human *papillomavirus* (HPV), have been linked to squamous cell carcinoma in the skin.

Numerous phytochemicals possess antimicrobial properties by interacting with microbial membranes. These compounds embed themselves in the lipid bilayer, resulting in:

- Enhanced membrane permeability
- Release of intracellular components
- Cellular lysis and subsequent death

A notable example is allicin, derived from garlic, which interacts with thiol groups present in membrane proteins, thereby compromising the structural integrity of bacteria.

Biofilms represent complex microbial communities encased within a protective matrix, making them notoriously difficult to eradicate with traditional treatments. Phytochemicals can play a crucial role in:

- Preventing the initial adhesion of microbes
- Disrupting mature biofilm structures
- Interfering with quorum sensing pathways that are essential for biofilm growth and the regulation of virulence factor production.

Notably, substances such as quercetin and berberine have been shown to inhibit gene expression regulated by quorum sensing, thereby lowering pathogenicity without necessarily killing the microorganisms, which helps to mitigate the development of resistance.

Individuals diagnosed with cancer, especially those undergoing chemotherapy or radiotherapy, are particularly vulnerable to infections due to compromised immune function and disruptions to the skin barrier. Incorporating phytochemicals with antimicrobial attributes may:

- Lower rates of infection
- Reduce the necessity for broad-spectrum antibiotics and the consequent side effects
- Improve overall treatment outcomes

Furthermore, phytochemicals that exhibit both antimicrobial and anticancer characteristics, like berberine and quercetin, have the potential to boost the effectiveness of traditional therapies while minimizing the risk of resistance development.

10. Photoprotective and Chemo preventive roles

Ultraviolet (UV) light, specifically UVB (290-320 nm) and UVA (320-400 nm), is a primary environmental carcinogen that causes and promotes skin cancer. UV exposure causes DNA damage by creating cyclobutane pyrimidine dimers (CPDs) and 6-4 photoproducts, leading to alterations in tumor suppressor genes including p53. Indirect DNA damage occurs when reactive oxygen species (ROS) are generated, resulting in oxidative stress, lipid peroxidation, and protein modification. Chronic UV exposure not only causes cancer, but it also promotes photoaging, inflammation, and immunosuppression, all of which contribute to tumor progression.

Phytochemicals have emerged as promising natural agents for preventing UV-induced skin damage.

These mechanisms are

- UV radiation absorption: Some chemicals, such as flavonoids, can act as natural sunscreens, absorbing UV rays and preventing them from accessing deeper skin layers [23].
- Antioxidant activity: Phytochemicals neutralize UV-induced ROS, which reduces oxidative DNA damage and cellular stress.
- Enhancement of DNA repair: Some phytochemicals activate nucleotide excision repair pathways, allowing cells to more efficiently correct UV-induced DNA damages.

Photoprotection via UV absorption and DNA repair help to build cellular defenses.

11. Challenges and Future Perspective

11.1. The bioavailability and stability of phytochemicals.

One of the primary problems in the therapeutic application of phytochemicals is their low bioavailability.

- Low aqueous solubility
- Poor absorption
- Rapid metabolism

These variables cause insufficient therapeutic concentrations in target tissues. Furthermore, environmental variables like light, heat, and pH can destroy phytochemicals, lowering their stability and effectiveness. Thus, improving the pharmacokinetic profile of these medicines is critical for their successful clinical implementation.

11.2. Nanotechnology and Delivery Systems.

Nanotechnology presents interesting possibilities to address the limits of phytochemical delivery. Approaches include:

- Polymeric or lipid-based nanoparticles
- Nanoparticles
- Nano emulsions
- Liposomes
- Solid lipid nanoparticles

The carriers can:

- Preserve phytochemicals from degradation.
- Improve the solubility and permeability.
- Enhance regulated and focused delivery.
- Increased circulation time in the body.

11.3. Integrating Phytochemicals into Standard Cancer Therapies

Combining phytochemicals with conventional therapies (chemotherapy, radiation, and immunotherapy) has various advantages.

- Synergistic effects: By regulating survival pathways, phytochemicals can make cancer cells more susceptible to chemotherapy and radiotherapy
- Reduced toxicity: Phytochemicals can shield normal cells from the negative effects of conventional treatments.
- Overcoming Resistance: Some phytochemicals can block medication efflux pumps and signaling pathways linked to therapeutic resistance.

To ensure safety and efficacy, dose, timing, and potential interactions with conventional medications must all be carefully considered.

11.4. Clinical Trails and Evidence Gaps

While several preclinical studies reveal phytochemicals' anticancer potential, clinical validation is sparse. Major challenges include:

- Lack of large-scale, randomized controlled trials.

- Variability in phytochemical sources, extraction techniques, and dosages
- Inconsistent outcome measures.
- Limited finance, commercial interest

Thus, well-designed clinical trials are urgently required to create uniform protocols, evaluate long-term safety, and validate efficacy in human populations [24]. Furthermore, regulatory standards for botanical-based cancer medicines must be devised to simplify their approval and implementation in clinical practice.

12. Conclusion

Skin cancer is still a serious global health concern, with an increasing occurrence due to genetic alterations, UV exposure, and other environmental factors. The CDK4 and BRAF genes are important in the progression of melanoma, the most malignant kind of skin cancer. Traditional Indian medicinal herbs, which are high in phytochemicals such as flavonoids, terpenoids, alkaloids, and organosulfur compounds, show great promise in skin cancer prevention and therapy due to their antioxidant, anti-inflammatory, antibacterial, and photoprotective qualities. Despite promising in vitro and preclinical findings, factors such as low bioavailability and inadequate clinical validation impede their therapeutic usage. Advances in nanotechnology and targeted delivery methods, as well as well-designed clinical trials, are required to convert these natural substances into effective, evidence-based cancer treatments.

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