Int J Adv Life Sci Res. Volume 7(3) 37-54
https://doi.org/10.31632/ijalsr.2024.v07i03.004

International Journal of Advancement in Life Sciences Research

Online ISSN: 2581-4877

Journal homepage http://ijalsr.org

Review Article

The Therapeutic Potential of Nutraceuticals in Modulating the Development of Skin Cancer

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Abstract

The integumentary system, including the skin, is essential to the human body. It acts as a crucial defensive mechanism against many environmental conditions, particularly prolonged exposure to sunlight that contains harmful ultraviolet radiation. Exposure to this factor initiates a series of events that ultimately damage the genetic material in skin cells, leading to unregulated cell proliferation and the subsequent formation of skin malignancies. The UV spectrum consists of two main categories, UVA and UVB, each having different effects on the skin environment. They cause cellular stress and directly damage DNA. A growing academic discussion focuses on understanding the effects of different diets on skin health, specifically comparing the Western diet, which includes a lot of processed food, with the Asian diet, encompasing natural and plant-based remedies. This variation in food habits has been suggested as a factor that affects the skin's general health. "Nutraceuticals" refers to substances derived from many sources that function as a powerful preventive barrier against developing and advancing skin tumors. Intentionally including nutraceuticals in one's diet, which entails precise enrichment with minerals, vitamins, and vital fatty acids, can improve skin conditions and strengthen the skin's resistance to cancer-causing propensities. This comprehensive review aims to clarify the complex relationship between skin cancers and the preventive potential of nutraceutical therapies, highlighting their beneficial effect in preventing the development of malignancies. The understanding gained from this research highlights the crucial importance of nutraceuticals and certain bioactive chemicals obtained from nature in promoting healthy skin and reducing the likelihood of developing malignant changes.

Keywords:- *Nutraceuticals, Skin cancers, Dietary choices, UV radiation, Skin health*

Introduction

The integumentary system, the largest organ within the human physique, plays a crucial role in safeguarding against environmental elements such as temperature, illumination, and microbial threats. Nevertheless, its vulnerability to many forms of harm is unquestionable (Muraleedharan *et al.,* 2023). Plant-based products, dietary choices, and nutraceuticals are crucial in averting skin cancer by incorporating antioxidants, vitamins, and compounds that shield against UV damage. These constituents boost skin health, reinforce the immune system, and diminish inflammation, thereby lowering the probability and severity of skin cancer through their preventive and rejuvenating

Received on :03rd April 2024; Revised version received on :20thJune 2024; Accepted: 30th June 2024

attributes (Saygi, 2023; Valigatla *et al.,* 2024). These substances improve the skin's condition, counteract the harmful effects of oxidative stress, shield against damage caused by UV radiation, and perhaps lower the likelihood of developing skin cancer (Gomaa, 2023). A significant part of skin damage may be specifically linked to extended exposure to ultraviolet (UV) radiation, mostly from sunshine. UV radiation has deleterious consequences that extend beyond mere skin diseases, substantially impacting genetic outcomes. UV radiation within the wavelength range of 200 to 400 nanometers induces dose-dependent photo-carcinogenic and photo-damaging effects. These factors include immunosuppression, acute inflammation caused by UVR exposure, defined by the presence of leukocytes in the skin, and erythema (sunburn) (Peterle *et al.,* 2023). Ultraviolet A radiation (UVA) has significant importance. The wavelength of this light spans from 320 nanometers to 400 nanometers and can penetrate both the epidermis and dermis to a depth of 1000 micrometers. The UVA component accounts for 90% to 95% of ultraviolet radiation (UVR). Ultraviolet A (UVA) induces oxidative stress and impairs the body's melanin manufacturing process, limiting its protective capacity against detrimental free radicals. Unlike Ultraviolet A radiation (UVA), Ultraviolet B radiation (UVB) and Ultraviolet C radiation (UVC) have a direct impact on DNA, resulting in damage. The epidermis, derived from the ectoderm, is the main outer layer that safeguards the organism and acts as a barrier between it and its external surroundings. The outermost layer of the skin, known as the stratum corneum, is composed of coenocytes and has a thickness ranging from 10 micrometers to 30 micrometers. The function of this layer is to protect the below levels. The main biological components, including keratinocytes, melanocytes, and Langerhans cells, reside underneath the stratum corneum. Keratinocytes, the predominant cells in the epidermis, have a vital function in preserving the structural soundness of the skin via the production of keratin, a hydrophobic protein. Concurrently, melanocytes, situated at the interface of the epidermis and dermis and inside hair follicles, generate melanin, a pigment that governs skin color and exerts several physiological effects. The purpose of melanin goes beyond pigmentation and includes regulatory control over the balance of the outer layer of the skin, the ability to remove harmful free radicals to reduce oxidative stress, and the capacity to operate as an antibacterial agent. The negative consequences of UV radiation exposure are diverse and include inflammation, immune system suppression, allergic disorders, increased sensitivity to UV radiation caused by drugs like corticoids, premature aging (photoaging), DNA damage, oxidative stress, and the gradual development of cancer. From a clinical perspective, these symptoms appear as skin redness, a sign of increased blood flow due to the widening of blood vessels near the skin's surface in the dermis (Mehdizadeh *et al.,* 2024). The term "nutraceutical" pertains to a naturally sourced product obtained from food or an element of food that possesses intrinsic medicinal properties. It combines the words "nutrition" and "pharmaceuticals." The scientific literature extensively documents a thorough compendium of 182 nutraceuticals derived from different spices. These nutraceuticals are derived from animals, microorganisms, and plants. They are naturally non-toxic and have bioactive properties that make them suitable for preventing diseases, promoting health, and being used in medicine. Nutraceuticals, when consumed as part of a diet, may have lower bioavailability and less effective dispersion in tissues compared to pharmacological medicines. Nutraceuticals' effectiveness is closely connected to the normal operation of liver phase II detoxifying metabolism and the gastrointestinal flora (Corsello *et al.,* 2023). The food and beauty industries are exploring novel approaches to understanding the connection between nutrient intake and skin well-being. Consequently, there is a growing tendency to utilize dietary components and supplements that reduce the likelihood of skin issues or improve the process of skin aging. Enhancing skin conditions by incorporating vitamins, essential fatty acids or minerals into one's diet is advisable. It is worth mentioning that most of the bioactive chemicals that have beneficial effects on health come from plants, while only a small portion is obtained from animals (van Amersfort *et al.,* 2023). The word "nutraceutical," introduced by Stephen DeFelice in 1989, denotes the convergence of the nutritional and pharmacological disciplines. DeFelice, the individual who established and held the position of chairman of the Foundation for Innovation in Medicine in Cranford, New Jersey, coined this newly created word. The dietary patterns often seen in Western countries are defined by the consumption of extensively processed fast food, dairy products with high-fat content, substantial quantities of red meat, and the use of sugary beverages. Conversely, the dietary regimen in Asian cultures is characterized by a low-fat, balanced diet that prioritizes whole grains, ample servings of vegetables and fruits, a relatively restricted meat intake, and a diverse range of spices. Moreover, several Asian nations extensively embrace natural plant-derived herbal remedies to preserve optimal well-being (Bommakanti *et al.,* 2023). Ayurveda and traditional Chinese herbal remedies are two significant medicinal systems. The many variables that contribute to the start of cancer include genetic predisposition, exposure to harmful substances, and hormonal imbalances (Patwardhan *et al*., 2005). Additionally, lifestyle factors such as food choices and nutritional habits play a significant role. Adhering to a diet that includes regular consumption of fruits, vegetables, foods rich in selenium, vitamin-enriched substances (especially B12 or D), folic acid, and antioxidants, along with increased fiber intake and controlled consumption of dairy products, plays a crucial role in specifically eliminating altered or malignant cells while causing no harm to healthy cells (Sable, 2023). Commonly eaten fruits and vegetables contain various beneficial compounds called polyphenols. These natural substances are found throughout the plant world. This group is very varied, with a documented inventory of over 8000 unique phenolic structures reported today (Saikia *et al.,* 2023).

Curcumin

Curcumin, a complex chemical produced from turmeric, has promising anticancer properties via various sophisticated methods. The comprehensive character of this approach strategically focuses on several aspects of cancer causation and development. One important aspect of its ability is its effectiveness in scavenging Reactive Oxygen Species (ROS), which are well-known for their significant role in the development and advancement of cancer. Novel curcumin analogs have significant promise in the treatment of cancer owing to their increased capacity to be absorbed by the body and better characteristics in terms of drug action when compared to natural curcumin (Konatham *et al.,* 2010). Curcumin significantly reduces oxidative stress by improving ROS levels, (Fig.1) which in turn helps prevent cellular damage that might lead to cancer development. In addition, curcumin significantly influences inflammatory responses, which is important considering the common connection between chronic inflammation and cancer development. The capacity to diminish inflammatory responses is of great significance, particularly in regulating pathways such as the Nuclear Factor Kappa Light Chain Enhancer of Activated B Cells (NF-κB), which governs genes associated with malignancy (Mushtaq *et al.,* 2023). Curcumin strategically lowers the production of pro-inflammatory mediators by blocking this pathway, preventing cancer-promoting microenvironments in the body. Another important aspect of curcumin's ability to fight cancer is its capacity to interrupt signaling molecules and transcription factors that promote cancer development. This directly hinders the series of signals that stimulate tumor growth and proliferation. Curcumin has shown its effectiveness in inhibiting the advancement of tumors in many models, such as a mouse skin cancer model, by both the application on the skin and ingestion. The translational significance goes beyond laboratory models to clinical studies, where orally delivered large dosages are safe for people with high-risk or premalignant lesions. Curcumin demonstrates its effectiveness at the cellular level by reducing the proliferation of skin cells, causing a halt in the cell cycle, and triggering programmed cell death in cancer cells. Studies conducted using the HCT 116, human colon cancer cell line, highlight the ability of curcumin to halt the cell cycle at certain stages, preventing uncontrolled cell growth (Pant *et al.,* 2023). Moreover, its ability to induce apoptotic cell death has great potential for selectively eliminating cancer cells. Essentially, curcumin has a variety of impacts on cancer cells, directly influencing their behavior. These properties, when combined, make curcumin a promising natural substance with significant promise for fighting cancer. Continuing research is gradually revealing the complex workings of curcumin, making it a promising candidate for advanced cancer treatments (Divyashree *et al.,* 2023).

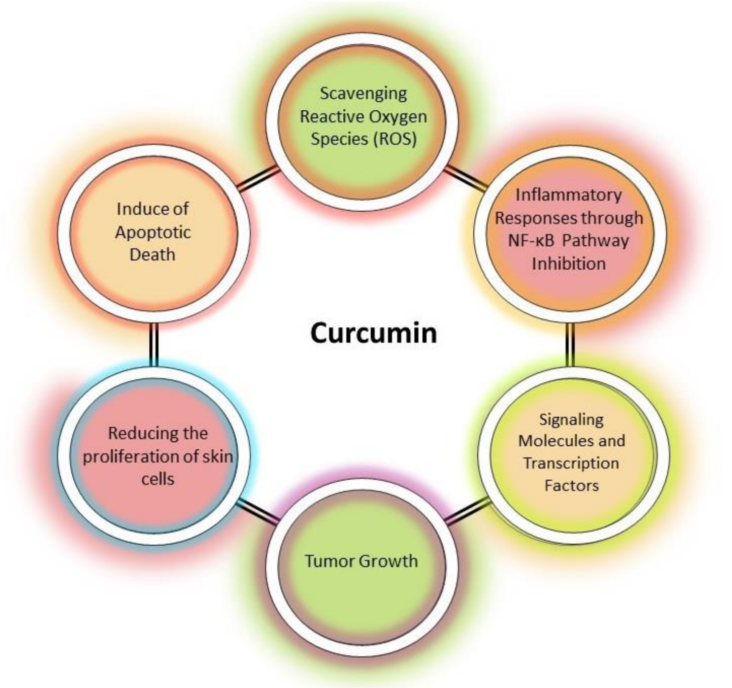

Figure 1: Curcumin Mechanisms of Cellular Regulation and Tumor Suppression

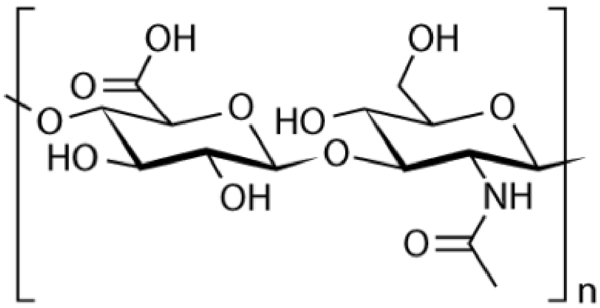

Figure 2: Glycosaminoglycans (Rousset *et al.,* 2006)

Polysaccharides with biological activity

Polysaccharides are complex sugar polymers that serve two important functions: providing structural support and storing energy. They are found throughout the biological world, including plants, mammals, fungi, and prokaryotic organisms. These molecules have diverse structural configurations, monosaccharide constitutions, and physicochemical properties, and they are present in various ways in biological systems. Glycosaminoglycans, derived mostly from marine sources, are considered the ideal substrate for nutraceutical formulations. This formulation includes protein fractions and specific glycosaminoglycans (Fig.2) obtained from marine fish sources. Vitamin C and zinc gluconate are included to complement these ingredients since they are recognized for their crucial functions in promoting skin health. A double-blind study rigorously evaluated the efficacy and safety of Vivida® with Imedeen®. The final findings demonstrated that both methods significantly changed several skin metrics, such as the depth of the epidermis and dermis, flexibility, and the erythemal index. Vivida® demonstrated superior effectiveness to Imedeen® in all evaluated areas (Cunningham, 2002). Imedeen® demonstrated substantial gains in fine lines, general premature aging, self-evaluation of skin quality, density, trans-epidermal water loss, and skin smoothness. Nevertheless, it is crucial to acknowledge that the duration of the treatment study was extensive. The extended duration of this timeline, which is an essential part of the investigation plan, deserves careful consideration and contextualization for interpreting the observed results.

Pycnogenol is a substance

Botanical extracts are complex combinations of naturally occurring substances with varied structures and come from many sources. Their historical use in cosmetics and skincare, which dates back to ancient times, has been extensively examined in existing literature (Usman *et al*, 2023). Polyphenols are crucial in these extracts, displaying significant diversity in their structural composition and classification within families. An outstanding example is Pycnogenol®, a highly standardized extract obtained from the bark of French maritime Pine. It contains many flavonoids, including catechins, (Fig. 3) procyanidins (Fig.4) and phenolic acids, such as caffeic, ferulic, and p-hydroxybenzoic acids. Scientific studies have definitively shown the many biological and physiological benefits associated with Pycnogenol®. These include improvements in cardiovascular health and cholesterol levels, antioxidant characteristics, effectiveness in managing diabetes, and anti-inflammatory capacities (Peterle *et al.,* 2023). Significantly, the consumption of Pycnogenol® has been scientifically linked to an observable increase in mRNA expression levels of hyaluronic acid synthase and simultaneous activation of genes that coordinate the production of new collagen. The application of Pycnogenol® from an external source has shown a considerable improvement in skin moisture and flexibility, as supported by statistical analysis ($p < 0.05$) (Tian, 2023). This confirms its significant potential as a pharmacologically effective and cosmetically beneficial botanical extract.

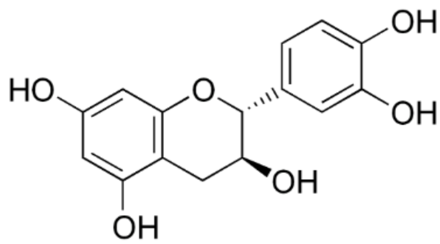

Figure:3 Catecins (Castaldo *et al.,* 2019)

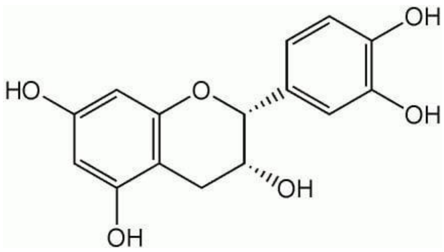

Figure:4 procyanidins (Majdan *et al.,* 2022)

Carotenoid

Carotenoids are biomolecules with inherent colors that naturally exist in several biological species, photosynthetic bacteria, algae, and plants. These living things possess a linear tetraterpenoid structure, which imparts hues ranging from red and yellow to orange. The digestive system mostly assimilates these compounds by ingesting fruits and vegetables. The primary pigments in our food are α-carotene, β-carotene, β-cryptoxanthin, lycopene, and lutein. The field of science thoroughly elucidates the efficacy of carotene supplementation in mitigating skin damage induced by ultraviolet rays in humans. This is corroborated by research that emphasizes their capacity to enhance the first signs of damage caused by UV rays in the dermis and the total magnitude of the injury. The study design lacked a placebo group. Nevertheless, the findings indicated a discernible, if small, rise in the minimum erythema dosage following the ingestion of daily quantities of sixty to ninety mg of carotenoids upon the dosage ($p < 0.05$). Concurrently, there was a rise in blood β-carotene concentrations after each dose and reduced plasma peroxidation of lipids. There was no observable β-carotene in the skin (Hyeraci *et al.,* 2023). Moreover, applying a moderate quantity of β-carotene before and after prolonged exposure to sunlight provided defense from sunburn. This is supported by a substantial decrease in inflammation on the skin and an increase in Langerhans cells ($p < 0.01$). These findings contribute to the growing body of research supporting the photoprotective capabilities of carotenoids and emphasize their possible use in preventive dermatology strategies.

Essential nutrients

Vitamins are chemical molecules that are necessary dietary components for humans. They are required in limited amounts and may be classified into several structural families. These substances significantly impact the skin's health, as explained by existing studies (Di Napoli *et al.,* 2023). Their diverse functions include antioxidant effectiveness, control of sebum and keratinization, production of collagen, preservation of extracellular matrix (ECM) balance, and supply of protection against sunlight exposure (Mehdizadeh *et al.,* 2023). A study was conducted with 60 healthy individuals, where a combination of vitamins obtained from fermented papaya (*Carica papaya* L.) and an antioxidant mixture was given. The observed results showed a significant improvement in skin elasticity, moisture content, and antioxidant capacity after applying the papaya preparation and the antioxidant cocktail. These improvements were statistically significant ($p < 0.05$). In a controlled study involving 33 participants, some were given 100 mg of vitamin C daily, some were given 180 mg of vitamin C per day, and some were given a placebo. The study lasted for 4 weeks. The results showed that taking 100 mg of vitamin C orally increased skin radical scavenging activity by 22%, while taking 180 mg of vitamin C increased antioxidant activity by 37% compared to the starting point. Although the photoprotective effects were detected in all groups that received supplements against sunburn cells at low UV irradiation, it is important to note that the limited size of the subject pool restricts the generalizability of these findings. Simultaneously, the photoprotective properties of vitamins E and C have been thoroughly examined. A rigorous investigation using a double-blind, placebo-controlled trial with a sample size of 20 participants has shown that the simultaneous administration of vitamins C and E has protective benefits. Significantly, this combination decreased the sunburn response, alleviated skin damage caused by UV radiation, and simultaneously regulated blood flow in the skin, in contrast to the placebo group, where these factors showed an increased trend (Lehr *et al.,* 2015).

Polyunsaturated fatty acids (PUFAs)

Well recognized for their beneficial effects on human health, polyunsaturated fatty acids have received dietary recommendations from several health authorities and institutes. Polyunsaturated fatty acids may be classified into omega-3 and omega-6 series depending on the arrangement of their double bonds. These PUFAs have significant biological effects that are particularly relevant to cardiovascular and inflammatory disorders and skin health. The oral supplement SemoSqualene® was given to a group of 40 healthy female participants who were over the age of 50. SemoSqualene® is known for its high content of squalene, an aliphatic hydrocarbon with polyunsaturated properties. After receiving a significant amount of squalene, ranging from 13.5 to 27 grams per day for 90 days, noticeable results included a decrease in facial wrinkles, reduced sensitivity of the skin to ultraviolet radiation, as shown by an increased Minimal Erythema Dose, increased activity of type I procollagen genes, and a decrease in DNA damage and cell death caused by UV exposure. The benefits might be attributed to the supplement's inherent antioxidant potential (McCarty *et al.,* 2023). In addition to fish oil, almonds are a significant source of omega-3 polyunsaturated fatty acids (PUFAs). These fatty acids consist of chains with at least eighteen carbon atoms, including a double bond located three atoms from the terminal methyl group. Consuming omega-3 PUFAs has been found to offer various therapeutic benefits, especially in treating skin inflammatory diseases. These fatty acids have shown anti-tumor effects on the skin by promoting cell cycle arrest and apoptosis, as well as reducing inflammation (Shahidi *et al.,* 2018). Changes in PUFA metabolism within cell membranes are associated with modifications in the structure and function of the dermal membrane, oxidative status, enzyme activity, and signaling pathways.Research by Dyerberg, Bang, and Hjorne highlighted the positive health effects of PUFAs, showing that high fish consumption, such as the Inuit and Danes, have lower rates of skin cancer and thus PUFA consumption was linked to a significantly lower risk of cutaneous malignant melanoma (Yang *et al.,*2018). Combining PUFAs with chemotherapy has demonstrated greater anti-tumor efficacy compared to doxorubicin alone in melanoma cells. Patients with cutaneous and mucosal metastatic melanoma treated with a PUFA–paclitaxel regimen had a 40% stable disease rate and a 10% partial response rate (Peterle *et al.,* 2023). CXCR4, a factor in the progression of cutaneous melanoma, is reduced in expression and stability by PUFAs, which also enhance the effectiveness of anti-cancer drugs like cisplatin (CDDP). Treatment with EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) makes melanoma cells more susceptible to CDDP-induced reduction in tumor growth and invasion. Omega-3 PUFAs also promote the production of improving the anti-tumor action of CDDP against cutaneous melanoma cells (Shahidi *et al.,*2018). Diffuse large B-cell lymphoma, a common type of non-Hodgkin cutaneous lymphoma, manifests as solid nodules or tumors on the skin, primarily affecting the extremities. A high intake of omega-3 PUFAs and seafood is associated with a lower risk of developing these non-Hodgkin lymphoma, while higher fat content in dietary products is linked to an increased risk (Peterle *et al.,* 2023). Studies indicate that patients with diffuse large B-cell cutaneous lymphoma who consume low levels of omega-3 fatty acids have poorer survival outcomes (Bakhshi *et al.,*2021).

Bergamot

Bergamot, scientifically called *Citrus bergamia* Risso & Poiteau, is a citrus fruit that grows primarily in the southern regions of Italy, namely along the Calabrian coast. The favorable cultivation of bergamot in this specific geographical area is made easier by the distinct climatic conditions that promote its development. From a taxonomic perspective, this citrus fruit is classified as a hybrid from crossbreeding a sour orange (*C. aurantium* L.) with either a lemon (*C. limon* L.) or a lime. Bergamot is present in its polyphenolic fraction (BPF) and juice (BJ), with the latter obtained by compressing the fruits formerly considered a byproduct.The impact of bergamot essential oil on human skin melanoma cells, triggered apoptosis (programmed cell death) and inhibited melanoma cell growth, stressing its potential as a treatment for skin cancer (Krasagakis *et al.,*1995). Further research provided more insights into how bergamot essential oil exhibits its anticancer properties. The oil influences several signaling pathways that are crucial for cancer cell proliferation and survival (Russo *et al.,*2015). The citrus bergamot fruit, indigenous to Calabria, Italy, is the source of the highly concentrated flavonoid extract known as the bergamot polyphenolic fraction (BPF). Research has shown that BPF has powerful antioxidant, anti-inflammatory, lipid-lowering, and metabolic properties, leading to improvements in cholesterol, blood sugar levels, vascular health, and insulin resistance (Nisticò *et al.,* 2016). Recent studies have examined the impact of 38% BPF on UV B-induced photoaging (Liu *et al.,* 2018). These investigations focused on the expression of inflammatory cytokines, changes in telomere length/telomerase activity, and cellular viability in human immortalized HaCaT keratinocytes from skin cancer patients (Mustafa *et al.,* 2024). Findings indicated that BPF significantly improved cell viability in a dose-dependent manner, with higher doses showing the least cytotoxicity when keratinocytes were pretreated (Omar *et al.,* 2010). UVB exposure caused approximately a 70% reduction in cell viability. Telomere signal alterations are closely associated with skin aging and cancer development (Trémezaygues *et al.,* 2009). BPF treatment resulted in a dose-dependent restoration of telomere length after radiation therapy, outperforming N-acetylcysteine(NAC) (Janeczek *et al.,* 2019). Polyphenols in food can inhibit telomerase, which is a crucial mechanism with potential anti-cancer effects. By reducing intracellular oxidative stress, BPF decreases DNA lesions in telomeres. Excessive UV radiation can overwhelm the skin's antioxidant defenses, allowing reactive oxidative species (ROS) to reach harmful levels and potentially cause skin cancer (Meng *et al.,* 2019). UV-induced oxidative stress generates damaging free radicals, contributing to the detrimental effects of both UVA and UVB. The antioxidant properties of BPF, due to the free radical scavenging action of hydroxyl groups on carbon aromatic rings, help reduce the incidence of cancer (Abd-ElSalam *et al.,* 2016).

Quercetin

The antineoplastic characteristics of quercetin, shown in laboratory experiments and live organisms, are closely associated with its ability to regulate the course of the cell cycle, induce programmed cell death, inhibit cell growth, impede the spread of cancer, and restrict the formation of new blood vessels. Quercetin regulates pathways associated with the tumor suppressor protein p53, simultaneously inhibiting the activity of cyclin-dependent kinase 2 (CDK2) and cyclins A and B. Quercetin derivatives, which make about 60% of the flavonoids taken daily, are the most important dietary flavonoids in the human diet. These derivatives are widely found in various vegetables and fruits, such as red onions, apples, berries (including cranberries, dark cherries, strawberries, and blueberries), olive oil, parsley, tea, cocoa, citrus fruits, and red wine. This highlights their widespread presence and importance in human nutrition. Estimates of daily quercetin consumption vary depending on dietary patterns, ranging from 5 to 40 mg per day. However, it may increase to 200-500 mg per day if particular drinks such as red wine and tea are consumed, along with a diet abundant in fruits and vegetables. Quercetin has been shown to have very low toxicity, as confirmed by investigations involving humans.These studies showed no negative effects even when single 4 g or 500 mg dosages were taken orally thrice daily. Furthermore, investigations suggest that there is no evidence of toxicity in people, even when consuming consumption amounts of up to 1 g/day (Riedt *et al.,* 2005).The specific formulation and concentration of cutaneous quercetin for the prevention or treatment of melanoma are yet unknown. However, evidence indicates that it has a physiologic effect on the skin, as shown by the improvement of radiation-induced skin fibrosis in C3H/HeN mice after taking it orally (Le Naour *et al.,* 2023). The lack of clinical studies investigating oral bioavailability, supplementation procedures, and mechanisms of action hinders the development of sensible therapeutic protocols using quercetin. Additional clinical trials are needed to determine quercetin's therapeutic potential despite its initial promise fully.The remarkable aspect is the scarcity of adverse effects linked to the consumption of quercetin by food or systemic injection, even at high dosages (Matyushina *et al.,* 2010). Therefore, quercetin has the potential to enhance the effectiveness of cytotoxic medications when used together, as long as concerns about its absorption into the body are resolved by chemical alteration or the use of an effective delivery method. Due to its significant influence on several signaling pathways and gene expression, quercetin is considered a valuable supplement to biological treatments. This compound not only enhances the therapeutic impact of drugs targeting specific pathways of signaling but it is also known to improve the efficacy of toxic therapies, such as a drug called, often used in cancer therapy (Seshacharyulu *et al.,* 2012). A recent study showed that quercetin improved the effectiveness of glioma therapy compared to standard radiation therapy by inhibiting the PI3 kinase–Akt pathway (Li *et al.,* 2016).

Ginger

The chemical analysis of ginger has shown the existence of over 400 physiologically active components. 6-gingerol, a complex synthetic molecule found in ginger, is now closely examined for its many pharmacological activities, including anti-inflammatory, antiangiogenic, antibacterial, and anti-carcinogenic effects (Haghighi *et al.,* 2017). 6-gingerol has shown significant effectiveness in treating several forms of cancer, such as colorectal, pancreatic, ovarian, breast, gastric, and cutaneous cancers (Surana *et al.,* 2023). Ginger and its bioactive components have been recognized as powerful suppressors of developing and forming new blood vessels in human ovarian cancer cells (Bharadwaj *et al.,* 2023). This substance's anti-inflammatory and antiangiogenic actions are attributed to its ability to inhibit nuclear factor-kappa B, reduce the production of interleukin-8 (IL-8), and decrease the secretion of vascular endothelial growth factor, a key component in angiogenesis. Moreover, 6-gingerol has shown cytotoxicity by inhibiting proliferation by stimulating reactive oxygen species in human epidermal carcinoma cells. The effectiveness of ginger in reducing the production of cytokines, ROS, and caspase activation generated by ultraviolet B has been confirmed by pre-treatment. Moreover, studies have shown that 6-gingerol might hinder the cellular transformation generated by epidermal growth factor and decrease the DNA binding activity of activator protein 1 induced by EGF. Surprisingly, when the ginger extract is applied directly to the skin of mice, it significantly prevents the activation of epidermal ornithine cyclooxygenase, decarboxylase, and lipoxygenase activities caused by 12-O-tetradecanoylphorbol-13-acetate. The study aimed to examine the antioxidant capacity of ginger extract when used as a daily supplement in recently diagnosed cancer patients receiving adjuvant chemotherapy (Galway *et al.,* 2012). Remarkably, the administration of ginger extract led to a substantial increase in the levels of antioxidant enzymes in the blood, namely superoxide dismutase 1 and catalase activity, as well as the levels of glutathione peroxidase and glutathione/glutathione disulfide. In contrast, there was a significant decrease in oxidative stress indicators, such as malondialdehyde and nitrite/nitrate. The cumulative data highlights the potential therapeutic benefits of ginger and its bioactive components in cancer prevention and treatment.

Garlic

Garlic is rich in sulfur-containing compounds, particularly allicin, and includes flavonoids, selenium, and arginine, all of which have substantial health benefits (Touloupakis *et al.,* 2010). Several studies have consistently shown a significant inverse relationship between the regular use of garlic and the probability of cancer development (Dorant *et al.,* 1996). Consuming more garlic has been linked to a decreased risk of getting several malignancies, including those that impact the stomach, esophagus, breast, pancreas, and skin (Mikolaskova *et al.,* 2023). The anti-metastatic effects of garlic's sulfur compounds, namely ajoene, have been elucidated (Dwivedi *et al.,* 2023). Research has shown that administering a dosage of 100 µg per animal of garlic substantially inhibited the production of tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), and levels of cytokines in the bloodstream. These findings indicate that garlic has potent anticarcinogenic and anti-inflammatory effects. Diallyl sulfide, a chemical present in garlic, has been associated with anticancer properties since it is believed to enhance the activity of several antimicrobial enzymes like superoxide dismutase (SOD), catalase, hemeoxygenase, and glutathione peroxidase. Consistent incorporation of garlic into a diet has demonstrated the ability to postpone the formation of skin papillomas and reduce both the quantity and dimensions of skin papillomas in mouse models (Khalil *et al.,* 2023). Furthermore, a meta-analysis has emphasized the significant benefit of ingesting a substantial quantity of allium plants in decreasing the occurrence of stomach cancer. The external application of garlic extract in dermatologists has considerable promise for treating many skin conditions. Research has verified that garlic-based gels are effective as a suitable adjunctive topical therapy for alopecia areata, a common dermatological disorder that causes hair thinning (Hajheydari et al., 2006).

Cloves

Cloves (*Syzygium aromaticum* L.), appears as dried, unopened flower buds. Cloves are highly valued for their versatility, as they may be used to enhance flavors and provide a distinct taste to dishes. Additionally, they are used in ayurvedic medicine for their therapeutic properties. The existing literature characterizes the makeup of these chemicals as an intricate blend of components, including sesquiterpenes, volatile oil (mostly eugenol), caryophyllene, tannins, and gum. The formation of bis eugenol, produced by the oxidative conversion of eugenol, has demonstrated a suppressive impact on the activation of NF-κB. This inhibition occurs by obstructing the breakdown of IkB produced by lipopolysaccharide (Nair *et al.,* 2023). Cloves have strong antioxidant qualities, effectively counteracting reactive oxygen species (ROS) and inhibiting the production of malondialdehyde (Khalil *et al.,* 2023). When mice with lung cancer generated by benzol(a) pyrene (108) were given a daily dose of 100 µl/mouse of clove infusion, there was a notable decrease in cell growth and activation of programmed cell death pathways. Cloves are believed to exert their chemo preventive effects by increasing the expression of proapoptotic proteins, such as p53 and Bax, while simultaneously reducing the expression of the antiapoptotic protein Bcl-2. Studies have shown that drinking clove infusion significantly decreases the occurrence of hyperplasia, dysplasia, and cancer. This highlights the infusion's capacity to suppress cell proliferation and trigger apoptosis. When mice were given a daily dosage of 100 milliliters of clove infusions in water, there was a decrease in the number and frequency of skin carcinomas. These data suggest that cloves may have a beneficial effect on the prevention of skin cancer. In experiments, administering 100 ml of clove aqueous infusion daily per animal led to a dose-dependent decrease in the incidence and number of mouse skin papillomas, indicating cloves' potential role in preventing skin cancer (Banerjee *et al.,*2005). Clove infusion significantly reduced the rates of hyperplasia, dysplasia, and cancer, highlighting its apoptogenic and antiproliferative effects (Haro-González *et al.,*2023). Eugenol, the primary ingredient in clove oil, is found in essential oils and many other plant extracts, such as those from nutmeg, cinnamon, and basil and has the ability to scavenge free radicals (Zari *et al.,* 2021) In vitro, eugenol reduced the generation of superoxide, and the metalloenzyme superoxide dismutase (SOD) protects cells from oxygen-mediated biological damage (Jayashree *et al.,* 1999). SOD is expressed at a low level during TPA-mediated tumor promotion, making eugenol's suppression of superoxide production significant in lowering the incidence of tumors. Topical application of eugenol, effectively diminishes inflammation in skin cancer by inhibiting the production of COX-2 and nitric oxide synthase (iNOS), decreasing the levels of proinflammatory cytokines such as TNF-α, PGE2, and IL-6, and modulating the expression of NK-κB (Wang *et al.,*2022). Eugenol can influence p53 expression, downregulate c-Myc and H-ras oncogenes, and reduce E2F1 transcription activity, all contributing to the induction of apoptosis (Ghodousi-Dehnavi *et al.,* 2021). In a study on skin carcinogenesis involving a cohort of female ICR/HA Swiss mice, the initiator 7,12-dimethylbenz(a)anthracene was applied topically three times a week for 63 weeks, with no carcinomas detected during this period (Crouch *et al.,* 1983). Eugenol inhibited papillomas induced by DMBA and croton oil by approximately 84% (Sukumaran *et al.,* 1994). Although eugenol increases sister chromatid exchange in Chinese hamster ovary cells, it is not mutagenic (Stich *et al.,* 1981).These findings suggest that cloves may have the ability to inhibit skin cancer progression. Although no clinical trials have been conducted on cancer patients to test its effectiveness, both laboratory and animal studies have shown cloves' potential as an anticancer agent.The apoptogenic and antiproliferative properties of clove showed a significant reduction in the frequencies of cancer, dysplasia, and hyperplasia (Rani & Jena, 2021). Cloves have been proven to have anticancer potential in laboratory and animal research, but no clinical trials on cancer patients have been done to test its usefulness (Putra *et al.,* 2024).

Rosemary

The rosemary extract is rich in polyphenolic compounds, namely diterpenes such as carnosic acid (CA) and rosmarinic acid (RA) (Da Silva *et al.,* 2023). At a dosage of 100 mcg/ml, the rosemary extract effectively eradicated 39% of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals. The proportion increased to 55% when the concentration of the extract was elevated to 500 mcg/ml. Furthermore, the extract exhibited an impressive 98% inhibition of liposome oxidation when used at 100 mcg/ml (Avhad *et al.,* 2023). Topical administration of rosemary extract in mice had significant inhibitory effects on the activity of ornithine decarboxylase induced by 12-O-tetradecanoylphorbol-13-acetate (TPA), as well as on inflammation, hyperplasia, and tumor promotion. The efficacy of rosemary and its primary derivatives in combating cancer is attributed to a variety of mechanisms, such as antioxidant activity, antiangiogenic properties, epigenetic modulation, immune response regulation, anti-inflammatory effects, hormone signaling alteration, specific metabolic pathway modification, and enhanced expression of oncosuppressor genes. Carnosol (CS) successfully suppressed the dissemination of highly metastatic mouse melanoma B16/F10 cells and notably reduced the tyrosine phosphorylation of various signaling proteins, including extracellular signal-regulated kinase (ERK) 1/2, p38, c-Jun N-terminal kinase (JNK), and AKT . Topical administration of a CS therapy before TPA treatment significantly reduced the formation of carcinomas in animals with DMBA-induced skin cancer. The inhibitory impact of the CS treatment on the TPA-induced activation of ornithine decarboxylase probably causes a decrease in activity. Tong *et al.,*investigated the advantageous chemopreventive characteristics of CS, showing its ability to diminish the increase of reactive oxygen species (ROS) induced by UVB radiation and the consequent DNA harm. Furthermore, the application of CS resulted in a decrease in the generation of cyclobutane pyrimidine dimers (CPD) in keratinocytes via the absorption of UVB radiation, hence mitigating the DNA damage induced by UVB exposure. In a mouse model of skin cancer induced by 7,12-dimethylbenz(a)anthracene, the oral administration of rosemary extract (RE) at doses of 500 or 1000 mg/kg/day for 15 weeks led to a significant reduction in the quantity, size, weight, and overall burden of malignancies. Furthermore, it increased the delay time compared to the control mice administered with DMBA (Baloghová *et al.,* 2023). The primary contributors to almost 90% of rosemary compounds' antioxidant capacities were carnosol and ursolic acid. Additionally, they exhibited potent inhibitory impacts on TPA-induced skin carcinogenesis. Carnosol impeded the mobility and penetration of B16/F10 murine melanoma cells by reducing tissue metallopeptidase activity (Martínez-Esparza *et al.,* 1998). Furthermore, administering rosemary extract orally to mice at 500 mg/kg body weight in a two-step procedure inhibited skin cancer formation. The extract's capacity to enhance glutathione levels is one of the factors contributing to its protective impact. Rosemary extracts have pharmacological and therapeutic effects that extend beyond skin cancer treatment. They can also be efficacious in treating colon, prostate, stomach, and breast cancers (Rahbardar *et al.,* 2020).

Table 1: Comparative Analysis of Bioactive Components, Pharmacological Activities, Mechanisms of Action, and Anti-Cancer Effects of Ginger, Garlic, Cloves, and Rosemary

Plant	Bioactive Components	Pharmacological Activity	Mechanism of Action	Anti-Cancer Effect	References
Ginger	Gingerol, Shogaol	Anti-inflammatory, Anti-oxidant,	Inhibition of NF-kB signaling, Induction of apoptosis,	Inhibition of cancer cell proliferation, Induction of apoptosis	Brahmbhatt *et al.,*2013
		Anti-cancer	Inhibition of angiogenesis	and differentiation, suppression of metastasis	El Fagie *et al.,*2021
Garlic	Allicin, Alliin	Anti-microbial,	Modulation of enzymes involved in carcinogen activation,	Induction of apoptosis, inhibition of angiogenesis,	Hussein *et al.,*2017
		Anti-oxidant,	Regulation of cell cycle progression,	inhibition of metastasis	Thomson *et al.,*2003
		Anti-cancer	Induction of apoptosis		Upadhyay *et al.,*2017
Cloves	Eugenol	Anti-inflammatory, Anti-microbial,	Inhibition of COX-2 and iNOS expression,	Induction of apoptosis, inhibition of angiogenesis,	Bachiega *et al.,*2012
		Antioxidant activity	Induction of apoptosis,	suppression of metastasis	Gülçin *et al.,*2012
		Anti-cancer,	inhibition of cell proliferation		Abadi *et al.,*2022
Rosemary	Carnosic acid, Rosmarinic acid	Anti-inflammatory, Anti-microbial, Anti-oxidant, Anti-cancer	Antioxidant activity, Modulation of signaling pathways involved in cell proliferation and apoptosis	Induction of apoptosis, inhibition of angiogenesis, suppression of metastasis	Arranz *et al.,*2015

Ginger, garlic, cloves, and rosemary are well-known for their culinary uses and medicinal properties. These herbs contain bioactive compounds such as gingerol, allicin, eugenol, and carnosic acid, which exhibit anti-inflammatory, antimicrobial, and antioxidant activities. In addition, they show promising anticancer effects through various mechanisms, including the inhibition of cancer cell proliferation, induction of apoptosis, and suppression of angiogenesis and metastasis. The bioactive components in these herbs target key pathways involved in cancer development and progression. Their potential in modulating skin cancer development makes them promising candidates for further research and development of novel therapeutic approaches (Table 1).

Saffron

Saffron, (*Crocus sativus L.),* is a spice obtained from the flower of the saffron crocus, a plant indigenous to Southwest Asia. Over 150 bioactive components have been found in saffron via thorough chemical analysis. Studies have shown a correlation between consuming carotenoids in one's diet and powerful anti-tumor properties. The relationship between carotenoids and their anticarcinogenic efficiency is based on their capacity to block the activation of inflammatory cytokines. Saffron prevents various cancers, including gastric, colorectal, hepatic, pancreatic, prostate, breast, cervical, ovarian, and skin malignancies. Research on aqueous saffron solutions has shown their ability to inhibit the progression of chemically caused skin cancers in mice. Saffron infusions have been associated with elevated levels of antioxidants, including glutathione S transferase, catalase, superoxide dismutase (SOD), and glutathione peroxidase. Furthermore, the consumption of saffron has shown inhibitory effects on the development of skin tumors and a concurrent decrease in the size of tumors in mice (Ashique *et al.,* 2023). This implies that the anti-cancer impact might be ascribed to the activation of cellular defense systems. Crocetin, a carotenoid molecule obtained from saffron, is hypothesized to function as a powerful anticancer agent. The effectiveness of crocetin is based on its essential mechanisms, which include suppressing the synthesis of DNA, RNA, and proteins and impeding the function of the RNA polymerase II enzyme in transformed cells (Balakrishnan *et al.,* 2023). Comprehensive laboratory and animal research have established the efficacy of the substance and crocetin in treating human cancers (Mishra *et al.,* 2023).The protective effects of saffron extract against UVB-induced skin damage and carcinogenesis in animal models were reported (Sharma *et al.,*2018). These studies collectively suggest that saffron possess significant anticancer properties, with potential applications in preventing and treating skin cancer. MBA/croton oil induced inflammation and oxidative stress-related DNA damage in skin leading to skin papilloma. DMBA makes an adduct with genomic DNA (Moschel *et al.,* 1977) that might play a role in the promotion and progression of skin carcinogenesis, causing cell proliferation and angiogenesis which was cured by topical application of saffron (Frenkel *et al.,* 1995). Studies in animal models and with cultured human malignant cell lines have demonstrated anti-tumor and anti- cancer activities of saffron (Abdullaev and Espinosa-Aguirre, 2004). The antitumor and anti-carcinogenic activity is attributed to inhibition of synthesis of DNA and RNA, but not protein (Abdullaev and Frenkel, 1992). Saffron treatment delays the formation of skin tumor papilloma growth and ascites and decreases the incidence of squamous cell carcinoma (SCC) and soft tissue sarcoma in mice, prolonging their life in comparison to untreated controls (Das *et al.,* 2004). Oral administration of aqueous infusion of saffron was found to produce a remarkable reduction in the incidence of mouse skin papilloma which is a pre-neoplastic benign growth. Topical application of saffron extract was also reported to inhibit skin carcinogenesis and oral administration of saffron extract in the same dose reduced 20-methylchloanthrene (MCA) induced soft tissue sarcoma in mice (Salomi *et al.,*1990).

Discussion

Nutraceuticals' has significant potential in both preventing and managing occurrences of skin cancer, complementing traditional treatments. Derived from natural sources, nutraceuticals offer a holistic approach to improve skin health and reducing cancer risk. It is evident that dietary choices impact these outcomes, as seen in the contrasting eating habits between Western and Asian populations. Curcumin, derived from turmeric, exhibits potent anticancer properties by scavenging reactive oxygen species, reducing oxidative stress, and modulating inflammatory responses (Kahkhaie *et al.,* 2019). Its ability to disrupt cancer-promoting pathways and induce apoptotic cell death positions it as a promising agent for advanced cancer treatments. Polysaccharides, including glycosaminoglycans found in Vivida® and Imedeen®, improve skin metrics such as dermal depth, flexibility, and erythemal index, with Vivida® showing superior efficacy (Yao *et al.,* 2002). Pycnogenol®, sourced from French maritime pine bark, enhances skin hydration, flexibility, collagen production, and offers potent antioxidant and anti-inflammatory benefits (Grether-Beck *et al.,* 2016). Carotenoids, present in various sources, mitigate UV-induced skin damage by enhancing the minimum erythema dosage, reducing lipid peroxidation, and alleviating skin inflammation, underscoring their importance in skin protection (Balić *et al.,* 2019). Vitamins, crucial for skin preservation and protection, enhance elasticity, moisture retention, and antioxidant defenses through formulations like vitamin-rich papaya extracts and antioxidant blends.Polyunsaturated fatty acids (PUFAs), improves skin health by reducing wrinkles, enhancing UV resilience, and boosting collagen production through their antioxidant properties (Nguyen *et al.,* 2012). Bergamot, containing unique flavonoids and glycosides like BEO and BPF, offers potential health benefits including anti-inflammatory effects and metabolic support. Quercetin, abundant in fruits and vegetables, has skin anticancer activity due to modulation of cell cycle pathways, potentially enhancing cancer therapy outcomes (Perna *et al.,* 2019). Ginger's bioactive compound, 6-gingerol, demonstrates potent anticancer effects through anti-inflammatory and antiangiogenic properties, suggesting it as a beneficial adjunct in cancer prevention and treatment. Garlic, cloves, and rosemary possess powerful natural compounds with anticancer properties. Garlic's sulfur compounds and diallyl sulfide inhibit cancer-related inflammation Cloves, rich in eugenol, demonstrate preventive effects across various cancers (Shukla *et al.,* 2007). Rosemary's carnosol and rosmarinic acid exhibit antioxidant and anti-inflammatory actions, effectively inhibiting skin cancer development. Saffron contains carotenoids like crocetin, which inhibit cancer cell proliferation and enhance antioxidant levels, displaying potent anticancer properties (Johnson *et al.,* 2011). Incorporating specific nutraceuticals, such as antioxidants, vitamins, and essential fatty acids, can mitigate UV radiation and oxidative stress on the skin, thereby reducing the risk of skin cancer. Nutraceuticals exert protective effects by enhancing the skin's natural defense mechanisms, reducing inflammation, and promoting DNA repair processes. The therapeutic potential of plant-based compounds in modulating gene expression linked to skin cancer development is vital (Katiyar *et al.,* 2007). Overall, the review advocates for integrating nutraceuticals into regular dietary regimens as a proactive measure against skin cancer. Further studies are encouraged to explore these compounds' efficacy in clinical settings and establish standardized guidelines for their application in cancer prevention (Katta *et al.,* 2015)

Conclusion

This review explores the intricate relationship between skin cancers and nutraceutical therapies within the context of dietary choices. Emphasizing the skin's role as a crucial defense mechanism against environmental factors, especially harmful UV radiation, the study delves into the damaging effects of UVA and UVB on genetic material, leading to unregulated cell proliferation and skin malignancies. The study underscores the importance of nutraceuticals and bioactive chemicals from natural sources in promoting healthy skin and reducing the risk of malignant changes. The intentional inclusion of these elements in one's diet emerges as a promising strategy for skin health maintenance and preventing skin cancer development. The focus on incorporating minerals, vitamins, and essential fatty acids in the diet underscores their potential to enhance skin conditions and strengthen resistance to cancer-causing tendencies.

Acknowledgements

The authors express their gratitude to the management of Surya Group of Institutions for their support and encouragement.

Conflict of Interest

All authors declare no competing interests.

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