Efficacy of herbal medicine as adjunctive therapy for skin cancer
Norbayu Mansor¹, Julia Joseph¹, Rolla Al Shalabi¹, Nozlena Binti Abdul Samad¹*

Abstract
Skin cancer is a condition in which the skin's cells grow abnormally. Skin cancer is one of the most common types of cancer worldwide. It is more frequently found in locations exposed to sunlight, although it can also occur in areas that are not normally exposed to sunlight. Numerous studies have investigated the efficacy of herbal medicine as an adjuvant therapy for skin cancer. Herbal medicine utilises plants, or combinations of plant extracts, to treat illness and promote health. Herbal medicine has grown in popularity over the last few decades due to its critical role in cancer prevention and therapy. As a result, herbal treatments are increasingly being studied and utilised extensively to treat skin cancers worldwide. This article aims to discuss the anticancer capabilities of herbal medicine as an adjuvant therapy for skin cancer, as well as the potential for their bioactive components to increase immunity and kill cancer cells. Additionally, this study will present an overview of anti-cancer compounds produced from plants that have been proven to have potential anti-carcinogenic characteristics in various skin cancer cell lines and animal models. This review aims to increase awareness of herbal medicine as adjuvant therapy for cancer and to provide further data for developing more effective anti-cancer medicines. Research utilising herbal medicine in various forms and at various levels in the future with more carefully designed studies will need to be conducted, including rigorous quality control and standardised models at the cellular, organic, animal, and clinical levels in order to combat skin cancer.

Keywords: Skin cancer, herbal medicine, adjunctive therapy, melanoma

Introduction
Skin cancer is the most common type of cancer. Skin cancer is the uncontrolled proliferation of aberrant cells in the epidermis, the outermost layer of the skin, resulting from uncorrected DNA damage that results in mutations. These alterations increase the rate at which skin cells grow, resulting in malignant tumours (Craythorne and Al-Niami, 2017). Skin cancer develops in the epidermis, the outermost layer of the skin. The epidermis is composed of three distinct cell types: squamous cells, which are located just beneath the outer surface and serve as the skin's inner lining; basal cells, which produce new skin cells and are located beneath the squamous cells; and melanocytes, which produce melanin, the pigment that gives skin its normal colour and are located in the lower epidermis (McGrath et al., 2004). While under the sun, melanocytes produce additional melanin to help protect the skin's deeper layers.

UV radiation, which is found in sunshine and tanning bed lights, damages the DNA in skin cells significantly (Narayanan et al., 2010). Ultraviolet (UV) radiation exposure is the leading cause of...
skin cancer. UV exposure is responsible for over 95% of all skin malignancies. When unprotected skin is exposed to UV light, the structure and behaviour of cells can alter (Narayanan et al., 2010). The sun emits ultraviolet (UV) radiation. However, it can also be emitted by artificial sources such as solarium lights (sun beds). UV radiation is not visible or audible and does not affect temperature. It can result in sunburn, accelerated skin aging, and cell damage, all of which can contribute to the development of skin cancer (Craythorne and Al-Niami, 2017).

On the other hand, sun exposure cannot account for skin malignancies that develop on skin that is not regularly exposed to sunlight. This shows that other risk factors for skin cancer, such as exposure to hazardous chemicals or a weakened immune system, may exist (Craythorne and Al-Niami, 2017). A dark spot, lesion, open wound, or lump on the skin are all possible indications of skin cancer (Craythorne and Al-Niami, 2017).

Skin cancer is more prevalent in older adults, although it can also afflict young adults and children in rare circumstances. It is more prevalent in men than in women and is more widespread in the elderly (Gloster et al., 2006). In women, skin cancer is most prevalent in sun-exposed areas such as the scalp, face, lips, ears, neck, chest, arms, and hands, as well as the legs (Craythorne and Al-Niami, 2017). Additionally, it can grow on areas that are rarely exposed to sunlight, such as your hands, below your fingernails or toenails, and in your genital area. While skin cancer is more prevalent in those with fair skin, it can also occur in those with darker skin (Gloster et al., 2006). The most prevalent skin cancer warning sign is a change in the skin, such as a new mole, a new skin lesion, or a change in an existing mole. Individuals with skin cancer are more likely to have additional skin cancers, and those with a family history of skin cancer are at even greater risk (Marks, 2000). You can reduce your risk of developing skin cancer by limiting or avoiding exposure to ultraviolet light. In addition, examining your skin for odd changes can help you discover skin cancer early. Skin cancer is more likely to be successfully treated if it is detected early.

**Types of skin cancers**

Basal Cell Carcinoma (BCC), Squamous Cell Carcinoma (SCC), and Melanoma are the three main types of skin cancer. Non-melanoma skin cancers are the first two types of skin cancer (NMSC). The most common type of skin cancer is non-melanoma skin cancer (NMSC).

**Basal Cell Carcinoma**

“basal cell carcinoma” refers to a specific type of skin cancer. Basal cell carcinomas (BCCs) are uncontrolled, malignant growths of the epidermis’s basal cells (Rubin et al., 2005). Basal cell carcinoma begins in the skin’s basal cells, which regenerate new skin cells when the old ones die. Basal cell carcinomas typically present as a waxy or pearly lump, a flat, flesh-colored or brown scar-like lesion, or a scabbing sore or bleeding that heals and recurs (Wong et al., 2003). Basal cell carcinoma is most frequently detected on sun-exposed body areas, such as the neck and face. Basal cell carcinoma occurs less frequently on areas of the body that are generally sheltered from light, such as the genitals (Wong et al., 2003). It is most commonly caused by excessive sun exposure, although it can also occur in adults who received radiation therapy as children. This kind of skin cancer develops slowly and seldom spreads to other body parts (Kuijpers et al., 2002).

Most basal cell carcinomas are thought to be caused by prolonged exposure to ultraviolet (UV) radiation from sunlight (Narayanan et al., 2010). Avoiding the sun and wearing sunscreen can help prevent basal cell cancer. A mutation in the DNA of one of the skin’s basal cells causes basal cell carcinoma (Lear and Smith, 1997). The basal cells are found near the epidermis’s base, the skin’s outermost layer. Basal cells generate new skin cells. Older skin cells are pushed toward the skin’s surface, where they die and are sloughed off. A basal cell’s DNA directs the process of skin cell regeneration. DNA contains the instructions that tell a cell what to do. The mutation encourages the basal cell to proliferate rapidly and expand even during dormancy periods. The aberrant cells that amass over time can eventually develop into malignant tumors that manifest as skin lesions. If basal cell carcinomas (BCCs) are not detected and treated promptly, they can cause local damage. These malignancies can occasionally metastasize (spread), and in rare situations, they can be fatal (Telfer et al., 2008).

**Squamous Cell Carcinoma**

Squamous cell carcinomas (SCCs) are the second most common skin cancer (Rudolph and Zelac, 2004). Squamous cell carcinoma is caused by changes in the DNA of the flat, thin squamous cells found in the middle and outer layers of the skin (Rudolph and Zelac, 2004). The scalp, backs of hands, lips, and ears are the most prevalent locations for squamous cell carcinoma of the skin. However, it can manifest itself anywhere on the body, including the lips, the soles of the feet, and the genitals (Yan et al., 2011). In those with darker skin, squamous cell carcinoma is more likely to develop in areas of the skin that are not frequently exposed to the sun (Gloster and Neal, 2006). Squamous cell carcinoma might present as a solid red nodule or as a flat crusted lesion (Kwa et al., 1992). Squamous cell carcinoma is a rare kind of skin cancer that is rarely fatal, but can be aggressive. If left untreated, squamous cell carcinoma of the skin can grow quite large and spread to other parts of the body, posing major health problems (Rudolph and Zelac, 2004). Most squamous cell carcinomas are
Table 1. Efficacy of phytochemicals in herbal medicines as adjunctive therapy for skin cancer.

<table>
<thead>
<tr>
<th>Phytochemical</th>
<th>Source</th>
<th>Biological activity</th>
<th>Efficacy</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allyl sulfides</td>
<td>Garlic</td>
<td>Anti-oxidant, anti-inflammatory, and anti-proliferative.</td>
<td>Diallyl trisulfide (DATS) reduces melanoma cell proliferation by triggering apoptosis, which is associated with Bcl-2 and Bcl-xl, downregulation and caspase activation.</td>
<td>Zhou et al (2009)</td>
</tr>
<tr>
<td>Eugenol</td>
<td>Cloves, bay leaves, cinnamon, basil, nutmeg</td>
<td>Anti-cancer, and anti-tumor.</td>
<td>Reduced and delayed the incidence of papilloma (tumor) formation.</td>
<td>Sukumaran et al (1994)</td>
</tr>
<tr>
<td>Eupatilin</td>
<td>Wormwood herb, mugwort</td>
<td>Anti-proliferative, and anti-melanoma.</td>
<td>Eupatilin induced apoptosis in A375 melanoma cells, which inhibited cell proliferation of A375 melanoma cells. The cell cycle was stopped at the G2/M phase, which aided in the induction of apoptosis.</td>
<td>Al Shawi et al (2011)</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>Olive trees</td>
<td>Anti-oxidant, and anti-cancer.</td>
<td>In a mice study with UVB radiation, when olive oil is applied to the skin it will delayed the onset and lowered the incidence of skin cancer growth.</td>
<td>Budiyanto et al (2000)</td>
</tr>
<tr>
<td>Punicic acid</td>
<td>Pomegranate seed oil</td>
<td>Anti-cancer, and anti-tumor.</td>
<td>Pomegranate seed oil appears to be a safe natural product with the potential to be used as a topical skin cancer chemopreventive.</td>
<td>Hora et al (2003)</td>
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Melanoma

Melanoma is one of the most dangerous forms of skin cancer; it occurs when unrepaired DNA damage to skin cells (most commonly caused by UV radiation from the sun or tanning beds) results in mutations (genetic abnormalities) that allow skin cells to grow rapidly and form malignant tumors (Thompson et al., 2005). Pigment-producing melanocytes cause these tumors in the epidermis’s basal layer. Melanomas resemble moles, and some of them begin as moles. Melanomas are typically black or brown in colour, but may also be pink, red, purple, blue, or white (Schadendorf et al., 2015). Melanoma is hazardous because it is significantly more likely to spread to other places of the body if it is not detected and treated early enough. Melanocytes accrue genetic alterations that activate oncogenes, inactivate tumour suppressor genes, and hamper DNA repair pathways due to environmental exposure to ultraviolet radiation (UV light) combined with a genetic vulnerability. All of this results in melanoctye proliferation, blood vessel growth, tumour invasion, immune response evasion, and finally metastasis (Thompson et al., 2005). Melanoma can affect people of any skin tone. However, melanoma is more prevalent in darker skinned individuals’ palms and soles, as well as under their fingernails and toenails (Gloster and Neal, 2006). Reducing exposure to ultraviolet radiation can reduce the chances of developing melanoma.

Herbal medicine as adjunctive therapy

The World Health Organization (WHO) defines herbal medicine as “plant-derived materials or preparations” (which contain either raw or processed components from one or more plants) used for treatment or other health advantages in humans (WHO, 1998). Traditional herbal medicine enhances health while diagnosing, treating, and preventing disease. Clinical trials conducted worldwide demonstrated a high prevalence of herbal medicine use as an adjuvant treatment for cancer (Carmandy and Smith, 2011; Wang and Xiong, 2012).

Herbal medicine dates back to ancient societies. It entails using medicinal plants to treat disease and promote overall health and well-being (WHO, 1998). Plant-based medications offer a novel and frequently quite effective approach to treating pain and sickness (WHO, 2013). Over thousands of years, herbal medicine, a significant component of complementary and alternative medicine, has developed its own system of concepts, diagnostics, and therapies. Analytical and quality control advancements, as well as clinical research discoveries, are demonstrating the efficacy of herbal medicine in the treatment and prevention of disease. Herbal therapy has grown in popularity over the years, and its critical role in cancer prevention and treatment is widely recognised (Nobili et al., 2009). Numerous research has been published on the medicinal use of plants in the treatment and prevention of cancer (Efferth et al., 2007). According to the World Health Organization (WHO), about 80% of the world’s population uses herbal medicine in some form of health care (Ekor, 2014).

Adjunctive therapy is any type of therapy utilised in addition to the primary treatment. Adjuvant therapy’s major objective is to decrease the chance of cancer recurrence while simultaneously increasing the success of first-line treatment (Zhang et al., 2021).

<table>
<thead>
<tr>
<th>Ursolic acid</th>
<th>Rosemary, thyme, and basil</th>
<th>Anti-proliferative, anti-inflammatory, and anti-oxidant.</th>
<th>The formation of papillomas in mouse skin was delayed, and the number of tumors was reduced.</th>
<th>Tokuda et al (1986), Huang et al (1994) &amp; Ramachandran (2008)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withanolides</td>
<td>Indian ginseng (Withania somnifera)</td>
<td>Anti-cancer, anti-proliferative, and anti-inflammatory.</td>
<td>Induces apoptosis in melanoma cells by causing the formation of reactive oxygen species (ROS) and downregulating Bcl-2. In a murine melanoma model, a methanolic extract of Withania somnifera was observed to inhibit metastasis.</td>
<td>Zhang et al (2012), Kalthur et al (2009), Kalthur &amp; Pathirissery (2010), Leyon &amp; Kuttan (2004), Mayola et al (2011)</td>
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Cancer cells may occasionally remain after surgery. Cancer cells may potentially circulate in the bloodstream or lymphatic system. The cancer cells that are traveling do not show up on imaging investigations. If left untreated, they might spread to other organs and cause new malignancies. This article summarises the usefulness of herbal medicine derived from a variety of plants, vegetables, and herbs as an adjunct therapy for the management of skin malignancies.

**Herbal medicine in the treatment of skin cancer**

Skin malignancies can be treated successfully with various treatments, especially if they are detected and treated early in their development. However, receiving therapy in a hospital does not guarantee that skin cancer cells will be entirely eradicated. Thus, the phytochemicals included in herbal medicines used as supplementary therapy for skin cancer will aid in the reduction of cancer cell proliferation.

Numerous findings indicate that dietary botanicals such as broccoli, cabbage, garlic, citrus fruits, green tea, tomatoes, soybeans, onion, ginger, and berries, as well as medicinal herbs, have chemopreventive properties against cancer. Numerous compounds, including genistein (found in soybeans), lycopene (found in tomatoes), sulforaphane (found in asparagus), indole-3-carbinol (found in broccoli), and resveratrol (found in grapes and peanuts), are being investigated for cancer chemoprevention in preclinical and clinical trials. In addition, phytochemicals offer much potential in cancer prevention due to their safety, low cost, and oral absorption. This article discusses the methods of action of potential natural cancer-preventive drugs.

**Sulphides of allyl**

In garlic, the primary organosulfur compounds are allyl sulfides, which comprise diallyl sulfide (DAS), diallyl trisulfide (DATS), and diallyl disulfide (DADS). According to existing evidence, the chemopreventive benefits of these allyl sulphides on skin cancer are attributed to their anti-oxidant, anti-inflammatory, and anti-proliferative properties. However, the chemopreventive effect of allyl sulfides has been ascribed to several different mechanisms.

DATS was discovered to induce apoptosis in A375 and M14 cells in a time- and dose-dependent manner (Zhou *et al.*, 2009). The expression of Bcl-xl and Bcl-2 was decreased. Following DATS sensitization, we observed the release of cytochrome c and activation of the downstream effectors caspase-3, caspase-9, and PARP. According to this finding, DATS inhibits the growth of melanoma cells by inducing apoptosis, which is related with Bcl-2 and Bcl-xl downregulation and caspase activation. Bcl-2 and Bcl-xl downregulation and caspase activation by DATS are crucial steps in the apoptotic cascade. Therefore, DATS may be a viable therapy option for malignant melanoma.

**Alpinia**

Numerous Alpinia species extracts have been evaluated for their anti-cancer potential. In addition, a. galangal (greater galangal) and A. officinarum (lesser galangal) extracts have been examined for their anti-melanoma effects.

Alpinia galangal is a Zingiberaceae plant that is primarily found in Southeast Asia. It is cultivated in India, Egypt, Thailand, Malaysia, Indonesia, and China, as well as in other tropical and subtropical Asian countries. Herbs are frequently used in both traditional medicine and seasoning. The rhizomes contain essential oil. Bisdemethoxycurcumin and 1,7-bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one, both derived from A. galangal, have been found to significantly inhibit melanoma cell proliferation (*Lo et al.*, 2013). This investigation was also conducted on the B16-F10 cell line, which demonstrated that the inhibitor had a little influence on cellular tyrosinase activity and melanin content.

Galganin, an active flavonoid found in high concentrations in Alpinia, has been demonstrated to be cytotoxic to several cancer cell lines, including melanoma. According to Zhang *et al.*, (2013), galgamin, a chemical isolated from A. officinarum, inhibited cell proliferation and caused apoptosis via the mitochondrial pathway and activation of p38 MAPK. On the other hand, the precise cellular targets of galangin-induced melanoma cytotoxicity are unknown. Galangin significantly decreased the viability of B16F10 cells and induced apoptosis. According to this study, galangin suppressed B16F10 cell proliferation by causing morphological changes and the appearance of apoptotic characteristics. Galangin changed the potential of the mitochondria and activated caspasas. Simultaneously, p38 MAPK activation rose gradually and dose-dependently over time. The activation of p38 MAPK is a component of galangin’s apoptotic response in B16F10 cells. B16F10 cells were treated with varying concentrations of galangin for 24 hours. According to the data, low dosages (10 mol/L) of galangin induced a modest growth response as compared to untreated controls. Above a particular concentration, galangin significantly lowered the percentage of viable cells. Microscopical
examination revealed decreased cells and morphological defects following a 24-hour galangin treatment. Galangin-treated cells grew elongated, flattened, and shrunk. According to the findings, galangin lowered cell survival, altered cellular shape, and induced apoptosis in B16F10 melanoma cells. Galangin reduced B16F10 melanoma cell proliferation and induced apoptosis via the mitochondrial pathway. Galangin-induced apoptosis has been associated with prolonged p38 MAPK activation. These findings give fresh light on galangin’s molecular mechanisms and suggest that it may be useful in treating melanoma.

Curcumin

Curcumin (diferuloylmethane) is a polyphenol phytochemical derived from the rhizome of the golden spice turmeric (Curcuma longa). Curcumin is a polyphenol derived from the Curcuma longa plant used as an analgesic, antibacterial, anti-inflammatory, anticancer, and antioxidant (Perrone et al., 2015).

Jiang et al., (2015) demonstrated that curcumin promotes apoptosis and inhibits the development of melanoma cells. Additionally, curcumin altered the expression of apoptosis-associated proteins such as NF-B, p38, and p53. Three different melanoma cell lines (A375, MV3, and M14) were treated with varying concentrations of curcumin for 24, 48, 72, and 96 hours to determine curcumin’s ability to inhibit proliferation. As a control, the normal human lung fibroblast cell line MRC5 was employed. MTT assays were used to determine cell proliferation. Curcumin-induced growth inhibition in melanoma cells was time and dose dependent. After 48 hours, the curcumin IC50 concentrations for cultured melanoma cells (A375, MV3, and M14) were 8.29, 18.29, and 14.25 lM, respectively. At concentrations of 5–30 lM, no significant growth inhibition was seen in MRC-5 cells under comparable circumstances. Curcumin can thus be used to specifically inhibit melanoma cell multiplication while having no effect on normal cells at lower dosages. According to the findings, curcumin’s anti-proliferative and proapoptotic effects are achieved by suppressing the NF-jB and p38 MAPK signalling pathways and downregulating anti-apoptotic proteins Mcl-1 and Bcl-2, elevation of p53 and Bax expression, and caspase-3 and caspase-8 cleavage. Curcumin induces cell death in melanoma cells by inhibiting various signalling pathways. As a result, curcumin may possess anti-tumor activity and represent an attractive treatment option for melanoma.

Daidzein

Daidzein is a soy isoflavone highly soluble in alkaline settings and is classified as a phytoestrogen (Huang et al., 2008). Because topical treatment of daidzein provided good photoprotection in one investigation, it has been proven to have some chemoprotective properties in the skin (Lin et al., 2008). Isoflavones, one of the key families of phytoestrogens, have been shown to have anti-oxidative and photoprotective characteristics in cellular and mouse studies. The purpose of this work is to acquire a better understanding of isoflavone-mediated photoprotection by adopting a more human-like pig skin model.

In vitro investigations demonstrated that daidzein reduced the generation of hydrogen peroxide within cells, hence protecting keratinocytes. Numerous research have examined daidzein and genistein as synergistic cytotoxic agents, and the two isoflavones have been proven to work synergistically (Huang et al., 2008; Lin et al., 2008). Genistein was reported to decrease the proliferation of two metastatic melanoma cell lines, murine Kl735M2 and human WM45l, in a dose-dependent manner. Genistein was shown to promote G2/M arrest in both Kl735M2 and WM45l cells, whereas daidzein enhanced cell numbers in the S phase but decreased them in the G1 phase. The presence of melanin and morphological analyses revealed that genistein can induce the formation of dendrite-like structures in Kl735M2 and WM45l and the production of up to 80% more melanin. On the other hand, Daidzein decreased K1735M2 growth but did not affect differentiation in either K1735M2 or WM45l. These findings suggest that genistein and daidzein, both present in soybeans, might inhibit various malignant melanoma phenotypes via separate mechanisms and may be used to treat melanoma malignancy (Huang et al., 2008; Lin et al., 2008). However, Daidzein permeated the skin only in trace levels, as determined by in vitro diffusion tests and tape stripping using Franz cells (Huang et al., 2008). This inability of daidzein to penetrate the skin may explain why so little research has been conducted on its potential utility as a topical photo- and chemoprotectant.

d-Limonene

D-Limonene is a naturally occurring chemical found in citrus fruits such as lemons, limes, and oranges. The scientific evidence supporting the use of d-limonene as an anticancer nutrient, notably in the prevention and treatment of breast cancer, is extensive (Miller et al., 2013). Based on its known properties, it is hypothesised that d-limonene utilises its solvent properties to infiltrate tumour cells and directly alter cell signalling and/or free radical formation, hence encouraging apoptosis.

While significant human studies on d-limonene and skin cancer are lacking, some experimental data is intriguing. Chaudhary et al., (2012) reported that dlimonene had a beneficial effect on tumour burden in a DMBA/TPA-induced multistage mice skin carcinogenesis model. D-Limonene, a common monoterpen, is anti-proliferative, induces apoptosis, and acts as a chemopreventive. They discovered that the monoterpen increased apoptosis, inhibited oxidative stress, and activated Ras
signalling, D-limonene may exert its chemopreventive action during TPA-mediated amplification of DMBA-induced skin cancer in mice by suppressing inflammation, oxidative stress, and Ras signalling and producing a pro-apoptotic state. Furthermore, the researchers discovered that topical D-limonene therapy inhibits the Ras/Raf/ERK1/2 signalling pathway, increases pro-apoptotic state, and retards DMBA/TPA-induced mouse skin carcinogenesis by decreasing skin inflammatory responses (edema, hyperplasia and COX-2 expression). As a result, D-limonene exhibits a variety of substantial chemopreventive effects on the reduction of skin tumours, hence preventing the development of this type of papilloma.

3-gallocatechin-3-gallate epigallocatechin-3-gallate (EGCG)

Epigallocatechin-3-gallate [EGCG] is a stable and water-soluble member of flavonoids known as flavan-3-ols (Lu et al., 2013). The main sources of flavan-3-ols are green tea (Camellia sinensis), strawberry (Fragaria ananassa), cacao (Theobroma cacao), and red wine (Vitis vinifera), with green tea being the most plentiful (Batra and Sharma, 2013).

Green tea polyphenols (Camellia sinensis) have been shown to provide several health benefits, including the protection of UV carcinogenesis. Green tea’s most abundant and photoprotective polyphenolic component is epigallocatechin-3-gallate (EGCG). EGCG’s antioxidant activities have been extensively studied in various disease types. The oral administration of GTPs (a mixture of polyphenolic components isolated from green tea) in drinking water or the topical application of EGCG induces the immunoregulatory cytokine interleukin (IL) 12; the IL-12-dependent DNA repair following nucleotide excision repair mechanism; and the inhibition of UVB-induced skin tumour development in mice. Green tea’s anti-UV carcinogenic activities have been widely investigated in vitro and animals. GTPs added to mice’s drinking water have been shown to provide significant protection against UV-induced skin carcinogenesis in terms of tumour incidence, tumour multiplicity, and tumour size compared to mice not given GTPs (Katiyar and Katiyar, 2007). Mice given crude green tea water extracts as their primary source of drinking water had fewer tumours than mice not given green tea water extracts (Katiyar and Katiyar, 2007). In mice, GTPs in drinking water or EGCG administered topically to pre-existing cutaneous papillomas led in partial regression or tumour development reduction (Katiyar, 2011). Oral administration of GTPs or EGCG over an extended period or topical application of GTPs or EGCG had no discernible adverse effects. Green tea as the primary source of drinking water resulted in a 53% reduction in keratoacanthomas, papillomas, and squamous cell carcinomas produced by continuous UVB radiation in mice (Katiyar, 2011).

Nihal et al., (2009) presented a treatment that combined EGCG and interferon (IFN) and shown synergistic anti-proliferative effects in vitro and in vivo against human melanoma cells. The researchers studied the effects of EGCG and IFN (alone or in combination) on the proliferation of three melanoma cell lines (A-375, G-361, and Hs-294T) representing distinct stages of disease progression using Trypan Blue exclusion analysis. According to the statistics, both EGCG and IFN alone treatments dramatically reduced the number of proliferating cells. The combination of EGCG and IFN was found to have a more dramatic and statistically significant inhibitory effect on cell development in Hs-294T and G-361 cells than either drug alone, and the A-375 cells exhibited a similar pattern. Compared to the control, the G-361 cells were the most responsive to the combined therapy, with a 56 percent reduction in proliferating cells.

Additionally, another study demonstrates that EGCG is a promising option for use as a photoprotectant, in addition to its anti-carcinogenic properties. Skin photoprotection is critical for skin cancer prevention, and studies have demonstrated that EGCG has a high potential for protecting the skin from photoinduced damage, the primary cause of skin cancer. According to Sevin et al., (2007), topical administration of EGCG to rat skin thirty minutes before UVA exposure inhibited sunburn cell development. The sample contains 2% EGCG, which was synthesised in a hydrophilic ointment medium (USP XXIV). Twenty-four 12-week-old Wistar albino rats were divided into four groups of six rats each. The control group received no topical therapy and was not exposed to UV radiation. Groups II and III were established to investigate the acute effects of UVA on the skin, Group IV was established to investigate the efficacy of topical EGCG administered 30 minutes after UVA exposure, and Group V was established to investigate the efficacy of topical EGCG applied 30 minutes before UVA exposure. After 24 and 72 hours, we examined sunburn cells, leucocyte infiltration, dermo-epidermal activation, collagen changes, and elastic fibre diseases in all groups. SPSS 11.5 was employed for statistical analysis, and the chi-squared test was used to analyse parameters. Group IV results indicated a statistically significant decrease in sunburn cells and dermo-epidermal activation compared to Group II. Furthermore, group II demonstrated a significant increase in all parameters when compared to Group I, showing the effect of UV exposure alone, but Groups II and III showed no difference. Finally, these findings indicate that EGCG is protective when applied prior to UV A exposure but ineffective after UV exposure.

Eugenol

Eugenol (4-allyl-2-methoxyphenol) is a phenolic compound found in cloves, bay leaves, nutmeg, basil, and cinnamon. Both topical eugenol and oral administration of an aqueous infusion of
clove delayed and inhibited the growth of papilloma (tumours) in skin cancer-bearing mice (Sukumaran et al., 1994). Sukumaran et al., (1994) studied female Swiss albino mice. We divided the female Swiss albino mice into two groups of ten mice each. The first tumour develops in the control group at week 5, whereas the first tumour emerged in the eugenol-treated group at week 12. By the 16th week after therapy began, tumour formation had decreased significantly (P <0.001).

Additionally, Eugenol decreased the number of tumor-bearing mice used in the investigation. By week 16, all control mice had acquired tumours, whereas only 40% of eugenol-treated mice had developed tumours. At week 16, the control group had an average of 2.56 ±0.78 tumours per mouse, compared to the eugenol-treated group, which had an average of 0.4 ±0.50 tumours per mouse (P <0.001). Finally, by week 16, eugenol therapy had resulted in an 84 percent reduction in the average number of tumours per mouse.

Eupatilin
Artemisia is a genus comprising about 500 species of aromatic herbs and shrubs. According to Al Shawi et al., (2011), eupatilin, a flavonoid produced from Artemisia species, has been shown to inhibit cell proliferation, induce apoptosis, and enhance G2/M cell cycle arrest in human melanoma cells (Al Shawi et al., 2011). Eupatilin inhibited cell growth in A375 melanoma cells by inducing apoptosis. Apoptosis was partially induced by arresting the cell cycle in the G2/M phase. The percentage of cells in the G2/M phase increased from 8.82 percent in untreated cells to 21.70 percent and 29.86 percent in cells treated with 150 and 300 M eupatilin for 24 hours, respectively. Furthermore, the ratio of G2/M cells increased significantly in A375 cells compared to the negative control group, which was accompanied by a drop in the population of cells in the G1/G0 phase of the cell cycle. These results established that one of the methods by which Eupatilin inhibits A375 cell proliferation is by arresting the cell cycle at the G2/M phase.

Flavanoid
Saraca asoka flowers have been used in Ayurvedic (traditional Indian) medicine for a long period, most notably for their wound-healing abilities (Thilaga et al., 2020). Cibin et al., (2010) investigated the chemopreventive effects of flavonoids extracted from Saraca asoka flowers on 7,12 dimethylbenz(a)anthracene (DMBA)-induced skin cancer in mice. Saraca asoka flowers were gently cleansed and hung to dry in the shade. The dried material was then mashed and extracted in a soxhlet system with 85 percent ethanol. The extract was decanted, filtered, and distilled over a water bath to remove the solvent. Repeated extractions with petroleum ether (60–80 °C) and ethyl acetate eliminated low-polarity contaminants from the extract, including lipids, terpenes, chlorophyll, and xanthophyll. The ethyl acetate fraction included the majority of polyphenols, which comprise the flavonoid component.

The mice were separated into four groups of twenty each. The control group received DMBA + croton oil, the DMBA + FF of S. asoka (5 mg/kg body weight) + croton oil group received DMBA + FF of S. asoka (10 mg/kg body weight) + croton oil group received DMBA + FF of S. asoka (10 mg/kg body weight) + croton oil group received DMBA + FF of S. asoka (10 mg/kg body weight) + croton oil group received DMBA + FF of S. asoka (10 mg/kg body weight) + croton oil group received DMBA + FF of S. asoka (10 mg/kg body weight) + croton oil group received DMBA + FF of S. asoka (10 mg/kg body weight) + croton oil group received DMBA + FF of S. asoka (10 mg/kg body weight) + croton oil group received DMBA + FF of S. asoka (10 mg/kg body weight) + croton oil group received DMBA + FF of S. asoka (10 mg/kg body weight) + croton oil group received DMBA + FF of S. asoka (10 mg/kg body weight) + croton oil group. When the flavonoid fraction of S. asoka (FF S. asoka) was injected 30 minutes before croton oil was applied thrice weekly for 20 weeks, the number of tumours per mouse and the percentage of tumor-bearing mice were considerably reduced. Additionally, pretreatment with S. asoka decreased the time required for the first tumour to appear. Prior to croton oil (promoter) application, topical treatment of S. asoka extracts to mouse skin provided considerable protection against DMBA-induced tumour development, tumour promotion, and overall carcinogenesis. The number of tumours per mouse, the percentage of tumor-bearing mice, and the mean tumour volume are utilised to demonstrate the flavonoid fraction’s protective effects. The average number of tumours in group II was 6.9 1.2, while it was 4.4 1.1 in group IV. Finally, after topically applying S. asoka, the percentage of tumor-bearing mice was reduced to 71% at the conclusion of the experiment. This demonstrates that Saraca asoka extracts can be absorbed via the skin and activate a protective signalling pathway. A skin biopsy of mice given S. asoka flowers revealed no evidence of cancer. The flavonoid fraction of S. asoka was discovered to possess significant chemopreventive activity against DMBA-induced skin carcinogenesis.

Genistein
Genistein is a major isoflavone found in soybeans. Soy, Greek sage, Greek oregano, and ginkgo biloba extract all contain genistein. Genistein has been shown to have anti-oxidant and anti-carcinogenic capabilities in the skin (Wei et al., 2003) as well as protective properties against photo-damage in mice (Shyong et al., 2002). In addition, genistein has been found in mice experiments to inhibit skin carcinogenesis. Wei et al., (1998) demonstrated that genistein inhibited DMBA-induced and TPA-promoted skin carcinogenesis by treating SENCAR (sensitive to carcinogenesis) mice with 10 micromoles of topical genistein for one week.

Wei et al., (1998) shows that topical genistein significantly reduced the number and incidence of ultraviolet B-induced skin
tumours in hairless mice. Genistein successfully reduced the initiation and development of chemically caused cancer in a two-stage skin carcinogenesis model. The anti-initiation effects are assumed to be due to the inhibition of cytochrome P-450 mixed function oxidase, which suppresses bulky DNA adducts. Anti-promotional effects are mostly connected with anti-oxidative and anti-inflammatory pathways, downregulation of PTK activity, and expression of proto-oncogenes associated with cell proliferation. Genistein’s anti-promotional activity appears less dependent on polyamine synthesis pathway regulation. Although no studies on genistein’s effect on human skin cancer development have been published, a small study of six males indicated that genistein reduced UVB-induced photodamage (Wei et al., 2003).

Lignans
The lignans sesamin, sesamolin, and sesaminol are all abundant in sesame seeds. Sesame oil has a chemopreventive effect in a two-stage carcinogenesis mouse model of skin cancer. Sesamol, another of its ingredients, has also been demonstrated to have chemopreventive properties (Kapadia et al., 2002). Additionally, sesame oil applied topically protects the skin from UV radiation (Korać and Kambholja, 2011).

Acid oleic
Olive oil is extracted from the olive tree’s fruit. Olea Europaea is largely constituted of oleic acid, with trace amounts of palmitic and linoleic acids. Around 200 chemical components make up olive oil, including carotenoids, sterols, triterpenic alcohols, and phenolic compounds. The most prevalent antioxidants in olive oil are hydrophilic phenols. Extra virgin olive oil applied to the skin delayed the beginning and decreased the incidence of skin cancer growth in a mouse trial using UVB radiation (Budiyanto et al., 2000). This is most likely attributable to a decrease in the number of cells positive for 8-hydroxy-20-deoxyguanosine (8-OHdG) (a biomarker of oxidative stress and carcinogenesis).

Budiyanto et al., (2000) investigated the effects of olive oil on UVB-induced skin carcinogenesis in hairless mice due to its known antioxidiant properties. Mice were given extra-virgin olive oil topically before and after repeated UVB exposure. In comparison to UVB control mice, mice coated with olive oil had a delayed onset of UVB-induced skin malignancies. Furthermore, compared to the UVB control group, mice fed olive oil after UVB exposure had significantly fewer tumours per animal in the post-UVB group. The mean number of tumours per mouse in the UVB control, pre-UVB, and post-UVB groups was 7.33, 6.69, and 2.64 in the first experiment, and 8.53, 9.53, and 3.36 in the second trial. These findings imply that using olive oil topically following UVB exposure may effectively prevent UVB-induced mouse skin malignancies, possibly by reducing DNA damage produced by reactive oxygen species, and that the effective component may be UVB labile.

Proanthocyanidins
Grape seed oil is made from the seeds of the Vitis vinifera plant. It is high in phenolic compounds, fatty acids, and vitamins. Zhao et al., (1999) extracted proanthocyanidins from grape seeds that had been air-dried and ground into a powder. They discovered that proanthocyanidins contained in grape seeds had a significant inhibitory effect on UVB-induced skin tumour growth in SENCAR mice. Procyanidins in grape seed polyphenols have a high anti-tumor-promoting potential due to their considerable anti-oxidant activity. To summarise, grape seed polyphenols in general, and procyanidin B5-3′-gallate in particular, should be further explored to develop cancer chemopreventive and/or anticarcinogenic medicines (Zhao et al., 1999).

According to Mittal et al., (2003), mice fed proanthocyanidins had decreased tumour size (29–94 percent), tumour incidence (20–95 percent), and tumour multiplicity (46–95 percent) during UVB-induced stages of photocarcinogenesis. Grape seeds have been shown in mice to protect against photocarcinogenesis and the malignant conversion of papillomas to carcinomas. This protection is associated with an inhibition of UVB-induced LPO or photo-oxidative lipid damage and a decrease in tissue fat levels. Additionally, they discovered that photoprotection occurred as a result of antioxidant mechanisms both in vivo and in vitro.

Acetic acid
Punicic acid is frequently found in pomegranate seed oil. Hora et al., (2003) discovered that pomegranate seed oil (5%) significantly reduced tumour incidence and ornithine decarboxylase activity caused by 12-O-tetradecanoyl-phorbol-13-acetate (TPA) in a chemical-induced skin cancer model in CD1 mice. The findings indicated that pomegranate seed oil may potentially be a skin cancer chemopreventive agent.

During the 20-week promotion period, topical administrations of pomegranate seed oil (5%) significantly decreased the incidence of skin tumour formation, multiplicity of skin tumours, and ornithine decarboxylase activity. Thus, it seems likely that the pomegranate seed oil’s inhibition of ornithine decarboxylase was responsible for at least a portion of the chemopreventive impact. Punicic acid is abundant in pomegranate seed oil and suppresses prostaglandin synthesis by inhibiting cyclooxygenase (Cox 1 and Cox 2) and lipoxygenase, respectively. Pomegranate seed oil also inhibits phospholipase A2, an upstream eicosanoid enzyme generated by human prostate cancer cells. Because prostaglandins activate ornithine decarboxylase23 at extremely low concentrations, prostaglandin synthesis by pomegranate seed oil may also contribute to its inhibition of ornithine decarboxylase.

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and hence to its inhibition of skin cancer propagation. By and large, pomegranate seed oil appears to be a safe natural product with the potential to be utilised as a chemopreventive for skin cancer. Additional study, including clinical trials, is required to validate this notion.

**Diterpene phenolic**

Rosmarinus officinalis is a perennial herb commonly referred to as rosemary. It is anti-oxidant-rich due to the presence of phenolic diterpene and triterpene (Ngo and Head, 2011).

Carnosol, a phenolic diterpene, is the active component in R. officinalis extract. In a study by Huang et al., (2005), carnosol inhibited the migration of metastatic murine melanoma cells into a basement membrane gel. This result was attributed to the inhibition of MMP-9. Carnosol inhibits the (ERK) 1/2, AKT, p38, and JNK signalling pathways, as well as NF-kB and AP-1 binding activities, in B16/F10 murine melanoma cells. MMP-9 activity and expression are considered metastatic markers in changed cell lines. The results indicate that carnosol suppresses B16/F10 melanoma cells' lung metastasis by reducing NF-kB and AP-1 binding activity. As a result, the transcription of MMP-9 mRNA and the translation of MMP-9 protein are blocked, resulting in decreased MMP-9 activity in cells. These data support carnosol's potential for cancer metastasis therapy.

**Resveratrol**

Resveratrol, a phytoalexin antioxidant found in red grapes, has been shown to have anti-cancer and anti-inflammatory properties in treating various diseases and disorders, including skin problems. It has been demonstrated that resveratrol protects against ultraviolet light, oxidative stress, and cutaneous damage, including skin cancer. Because many skin disorders are induced by UV radiation and oxidative stress, this antioxidant appears to have promise and potential against a broad spectrum of cutaneous illnesses, including skin ageing and skin cancer. Resveratrol is a phytoalexin antioxidant that occurs naturally in grapes, berries, peanuts, and red wine (Ren and Lien, 1997). It is a trihydroxystilbene (3,4',5'-trihydroxystilbene) derivative.

Jang et al., (1997) investigate tumorigenesis using a chemically induced skin carcinogenesis mouse model and cultured mouse mammary glands treated with carcinogens. Since the publication of this article in 1997, a profusion of investigations, both in vitro and in vivo, have demonstrated that resveratrol could be developed as an effective chemopreventive and/or therapeutic agent for the management of cancer (Adhami et al., 2003; Afaq et al., 2003; Ahmad et al., 2001; Pezzuto et al., 2008).

Yang et al., (2008) shown that resveratrol can induce apoptosis in two human melanoma cell lines in vitro and that resveratrol significantly inhibits APE/Ref-1 and decreases the levels of AP-1/JunD, MMP-1, Bcl-2, and iNOS proteins in melanoma cells. Finally, when NO stress increases APE/Ref-1, a functional feedback loop is established that contributes to melanoma cell proliferation and metastatic capacity, which can be blocked by resveratrol.

**Ursolic acid**

Ursolic acid is a terpenoid molecule found in herbs such as thyme, rosemary, and basil. It is an anti-oxidant, anti-inflammatory, and anti-proliferative. In 1986, Tokuda et al. demonstrated that topical ursolic acid inhibits the formation of tumours in a mouse skin model. Each mouse's back was shaved with surgical clippers. The mice were initiated with dimethylbenz [a] anthracene (DMBA) (390 nmol) in acetone (0.1 ml). They were promoted twice weekly for one week after beginning using 12-O-tetradecanoylphorbol-13-acetate (TPA) (4.1 nmol) in acetone (0.1 ml). One hour prior to each TPA treatment, the animals were administered ursolic acid (OA), ursolic acid (UA), and retinoic acid (RA) (41 nmol) in acetone (0.1 ml). Prior to the initial TPA treatment, OA, UA, and RA were only applied once.

The inhibitory effects of UA and OA on TPA-induced tumour promotion were examined in a 20-week initiation-promotion assay in mouse skin. The activities were evaluated using both the rate (percentage) of papilloma-bearing mice and the average number of papillomas per mouse. Both UA and OA treatments, when given continuously before to each TPA treatment, decreased the formation of papillomas in mouse skin when compared to a control experiment utilising only TPA. Additionally, they decreased the number of mice with papillomas and the rate per mouse. Surprisingly, a single application of UA prior to the initial TPA-treatment significantly boosted activity over multiple applications.

Huang et al., (1994) reported a similar effect when rosemary and its ingredient ursolic acid were applied topically to animals with skin cancers, decreasing the number of tumours. In addition, ursolic acid exhibited photoprotective anti-oxidant activities in UVB-irradiated human lymphocytes, as pretreatment with ursolic acid reduced lipid hydroperoxide levels and increased anti-oxidant levels (Ramachandran et al., 2008).

**Withanolides**

Withania somnifera, also known as ashwaganda or Indian ginseng, is a Solanaceae plant that generates a class of medicinal compounds called withanolides. Two melanoma cell lines were treated with natural and derivative withanolides, and an anti-proliferative effect was seen (Zhang et al., 2012). Withaferin A (WA) is the most potent and well-studied withanolide, and Kalthur et al., (2009) proposed that WA may be beneficial in
treating melanoma with hyperthermia. Withaferin A increased tumour response and decreased thermotolerance during hyperthermia treatment (Kalthur et al., 2009). Following observations that a combination of hyperthermia, irradiation, and a non-toxic dose of WA produced a higher therapeutic response in a mouse model compared to radiation alone (Kalthur and Pathirissery, 2009), it has been suggested as a feasible alternative for melanoma therapy. A methanolic extract of Withania somnifera has been shown to inhibit metastasis in a mouse melanoma model (Leyon and Kuttan, 2004) but withaferin A alone induces apoptosis in melanoma cells by generating reactive oxygen species and downregulating Bcl-2 (Mayola et al., 2011).

Saffron

Saffron is made from the dried stigma of the Crocus sativus flower (family Iridaceae) (Abdullaev, 2002). According to Das et al., (2004), saffron medication inhibits the creation of tumour skin papilloma growth and ascites in mice, as well as the incidence of squamous cell carcinoma (SCC) and soft tissue sarcoma (Das et al., 2004).

In another study, Das et al., (2010) modelled the course of malignant skin cancer using 7,12 dimethylbenz[a]anthracene (DMBA) followed by croton oil. DMBA generates free radicals in the area of the skin where it is administered, leading in epidermal neoplasia, which is composed of an irreversible tumour initiating stage and a reversible but accumulative tumour promotional stage. In this study, the mice were divided into five groups: carcinogen control (CC), normal control (NC), and saffron-treated Groups A, B, and C. Mice in groups A, B, C, and CC received three topical treatments with 7,12 dimethylbenz[a]anthracene (DMBA) followed by croton oil on shaved dorsal skin for eight weeks. The vehicle, acetone, was administered only to the NC mice's skin. Saffron infusions were given orally to three groups of mice either prior to (Group A), following (Group C), or both DMBA treatments (Group B). At 0, 6, 10, and 12 weeks, we evaluated the antioxidant enzymes glutathione-S transferase (GST), catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD) in liver tissue samples from all groups. Saffron medication was administered to mice before and after skin carcinogenesis was induced, and routine histological assessment of the skin demonstrated that saffron has a beneficial effect. Saffron eating decreased the size and inhibited the growth of cutaneous papillomas in rats. According to the findings, saffron prevents DMBA-induced skin cancer in mice when given early. According to the findings of this study, saffron can inhibit cell proliferation and dysplasia, hyperplasia, and papilloma growth. Saffron consumption also inhibited microvessel formation in papillomatosis and SCC, implying that saffron may be used to prevent or delay tumour growth and angiogenesis. More research is needed to fully understand the molecular mechanisms of action of saffron compounds to establish saffron as an efficient cancer chemopreventive medication.

Conclusion

Oncogenic phytochemicals from plants are effective against skin cancer. Many herbal medicines contain phytochemicals that can help prevent and treat cancer. Phytochemicals can prevent cancer, even if they are not as effective as standard chemotherapies. Phytochemicals are well tolerated and easily available for skin cancer prevention and treatment. In addition, these natural compounds may help guard against and counteract the impacts of UV radiation and other contaminants.

Author Contributions

NM. JI, RAS, and NBAS conducted the review and wrote the paper.

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