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"Exploring Plant-Based Approaches for Melanoma Cancer Treatment: A Comprehensive Review"

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Abstract: Marine, microbiological, and botanical sources are among the many natural sources of anti-cancer medications. The most aggressive type of skin cancer, cutaneous malignant melanoma, has a high death rate, and multi-drug resistance complicates current chemotherapy treatments. It's critical to find safe and efficient chemicals to combat melanoma. The mechanisms of action of chemicals originating from plants are identified by in vitro research using murine models and melanoma cell lines. Natural compounds have anti-melanoma properties through metastasis inhibition, apoptosis promotion, and cell proliferation inhibition. Enhancing caspase activity, preventing angiogenesis, and opposing proteins that promote tumor growth, such as PI3-K, Bcl-2, STAT3, and MMPs, are some of the mechanisms. This article offers a summary of natural substances, such as flavonoids, carotenoids, terpenoids, vitamins, sulforaphane, polyphenols, and plant extracts, which are employed in cancer treatments or exhibit anti-melanoma properties. This overview provides information on the different kinds, causes, prevention, diagnosis, and therapy of melanoma.

Keywords: Melanoma cancer, proliferation, phytochemicals, anticancer properties, safety profiles.

INTRODUCTION:

Uncontrolled cell proliferation and spread throughout the human body are hallmarks of cancer. With trillions of cells, the body normally divides its cells in a controlled manner to produce new ones when needed. Cells naturally die when they get older or are damaged, allowing new cells to grow.

But occasionally, this well-organized mechanism can go wrong, causing injured cells to proliferate uncontrollably. Tumors from this unchecked growth can develop; these tumors might be benign or malignant (meaning they are not cancerous). Malignant tumors have the capacity to spread to other sections of the body and can infiltrate adjacent tissues. Solid tumors are common, though cancers of the blood, like leukemia's, usually do not manifest as solid masses.

Unlike cancerous tumors, benign tumors do not infiltrate neighboring tissues and are typically non-threatening. Removal of benign tumors often prevents their recurrence, whereas cancerous tumors may reappear after removal. Despite being non-invasive, some benign tumors, especially in critical areas like the brain, can pose serious health risks.

Cancer is a diverse group of diseases named after the body part where it originates. Staging assesses its spread.

TYPES:

There are five main types:

1. **Carcinoma:**
    - Originates in epithelial tissue.
    - Examples: skin cancers with squamous cells, basal cell carcinoma, and melanoma.
2. **Sarcoma:**
    - Malignant tumor from connective tissues.
    - Examples: Osteosarcoma, Ewing's sarcoma, and soft tissue sarcoma.

3. **Lymphoma:**
    - Originates in lymphatic system nodes or organs.
    - Types: Cutaneous lymphoma, Non-Hodgkin's lymphoma, and Hodgkin's lymphoma.
4. **Leukemia:**
    - Blood cancer affecting bone marrow.
    - Types: include acute myeloid leukemia, acute lymphocytic leukemia, chronic myeloid leukemia, and chronic lymphocytic leukemia.
5. **Myeloma:**
    - Grows in bone marrow's plasma cells.
    - Types: Multiple myeloma, Plasmacytoma.

Each type has distinct characteristics, and its name reflects its origin. Staging helps determine the extent of cancer spread.

Melanocytes, which are specialized cells that produce the pigment melanin, which defines skin color, are the source of melanoma, a dangerous form of skin cancer. The intricacies of melanoma underline its potential severity.

Predominantly emerging on sun-exposed skin areas like arms, back, face, and legs, melanoma can also manifest within the eyes and, albeit infrequently, internally, such as in the nasal or throat cavities. The causative factors for all melanomas remain elusive, though a significant proportion can be attributed to ultraviolet (UV) light exposure. This radiation, emanating from sunlight or artificial sources like tanning lamps and beds, poses a substantial risk.

Mitigating the risk of melanoma entails prudent measures to limit UV light exposure. Awareness of melanoma's increasing incidence in individuals under 40, particularly among women, prompts a more vigilant stance. Recognizing skin cancer symptoms becomes paramount for timely detection and intervention before metastasis occurs.

Vigilance in identifying potential signs of melanoma is crucial, as early detection significantly enhances treatment efficacy. Regular skin examinations and dermatological consultations are imperative for fostering a proactive approach to managing melanoma. In essence, understanding the nuanced aspects of melanoma, from its cellular origins to environmental triggers, empowers individuals to make informed decisions for their skin health and overall well-being.

Changes in pre-existing moles or the emergence of newly pigmented or odd-looking skin growths are frequently observed as early indicators of melanoma. Melanoma can manifest anywhere on the body, with frequent occurrences in sun-exposed areas like the arms, back, face, and legs. However, it can also develop in less exposed regions, such as the soles of the feet, palms, and fingernail beds. Additionally, melanoma may arise internally, more commonly in individuals with brown or black skin.

Typical moles are often round or oval in shape, have a defined border, are less than 1/4 inch in size, and are uniformly colored—often pink, tan, brown, or black. Most people develop between 10 and 40 moles by adulthood, with changes in appearance over time.

Signs indicating potential melanoma include asymmetrical shapes, changes in color or size (especially if larger than 1/4 inch), new symptoms like itchiness or bleeding, and moles with unusual borders. Different melanomas may display different atypical characteristics; some may show many modifications, while others may only show one or two odd features.

Hidden melanomas are melanomas that develop in less exposed, sun-exposed areas. These include mucosal melanoma inside the body's mucous membrane, eye melanoma in the uvea beneath the white of the eye, and acral-lentiginous melanoma under nails or on palms or soles. Detection of hidden melanomas may be challenging, emphasizing the importance of comprehensive skin examinations and awareness of potential symptoms for early diagnosis and effective intervention.

Melanoma arises when healthy melanocytes, the skin cells responsible for producing the pigment melanin, undergo genetic changes that transform them into cancer cells. These changes occur within the DNA of melanocytes, where instructions for cell behavior are encoded. In normal cells, DNA dictates controlled growth, multiplication, and programmed cell death. However, in cancer cells, alterations in DNA provide different instructions, prompting rapid and uncontrolled cell proliferation. Unlike healthy cells, cancer cells defy the natural cycle of cell death, leading to an accumulation of excess cells.

The aberrant growth may result in the formation of a mass known as a tumor, which can infiltrate and damage surrounding healthy tissues. Metastasis is the term for the process by which cancer cells separate from the main tumor and spread to different areas of the body over time.

The precise factors triggering DNA changes in skin cells and the subsequent development of melanoma remain unclear, most likely resulting from a synthesis of hereditary and environmental factors. Although exposition to ultraviolet (UV) radiation from tanning lamps or the sun is thought to be a main cause of melanoma, it does not account for all cases, particularly those occurring in areas of the body with limited sunlight exposure. This indicates that an individual's chance of acquiring melanoma may be influenced by other factors.

RISK FACTORS:

- **Family History:** higher risk if a sibling, parent, or other close relative has had melanoma.
- **History of Sunburn:** Severe, blistering sunburns raise the risk.
- **UV Light Exposure:** Sunlight and tanning lamps/beds heighten the risk.
- **Many or Atypical Moles:** Over 50 typical moles or atypical moles (dysplastic nevi) increase risk.
- **Geographical Factors:** Living closer to the equator or at higher elevations exposes individuals to more UV light.
- **Sun-Sensitive Skin:** Higher risk for those with white skin, blond or red hair, lightcoloured eyes, and a tendency to sunburn easily.
- **Weakened Immune System:** Medications, illness, or conditions like HIV can elevate the risk of melanoma.

PREVENTION:

- **Avoid UV Exposure:** Steer clear of tanning lamps/beds and limit sun exposure, especially during peak hours.
- **Skin Monitoring:** Regularly check for changes in moles, freckles, and skin growths.
- **Protective Clothing:** Wear dark, tightly woven clothing, a broad-brimmed hat, and sunglasses for sun protection.
- **Sunscreen Use:** Even on overcast days, use a broad-spectrum sunscreen with SPF 30 or higher, and reapply as necessary.

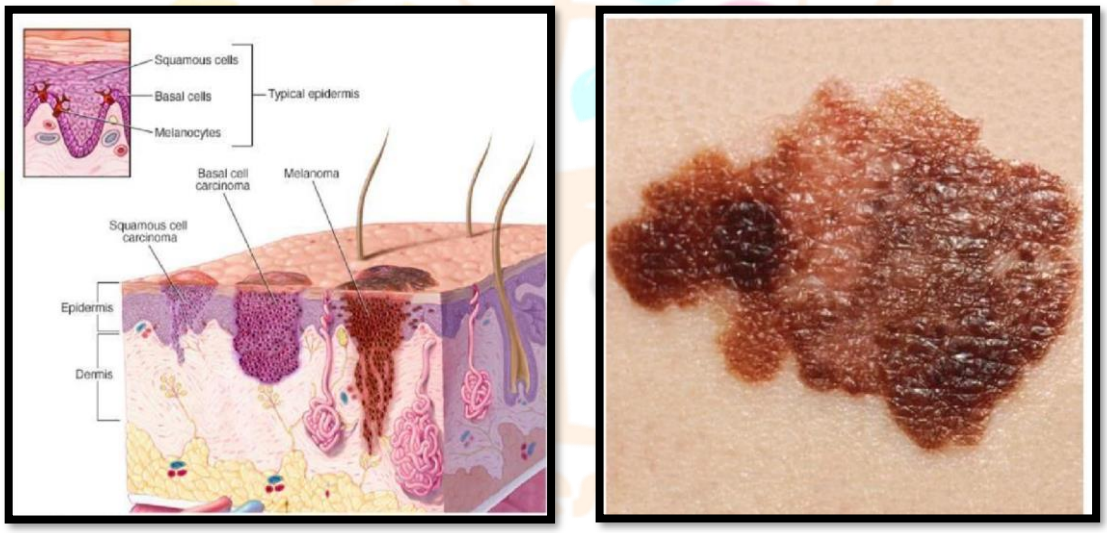


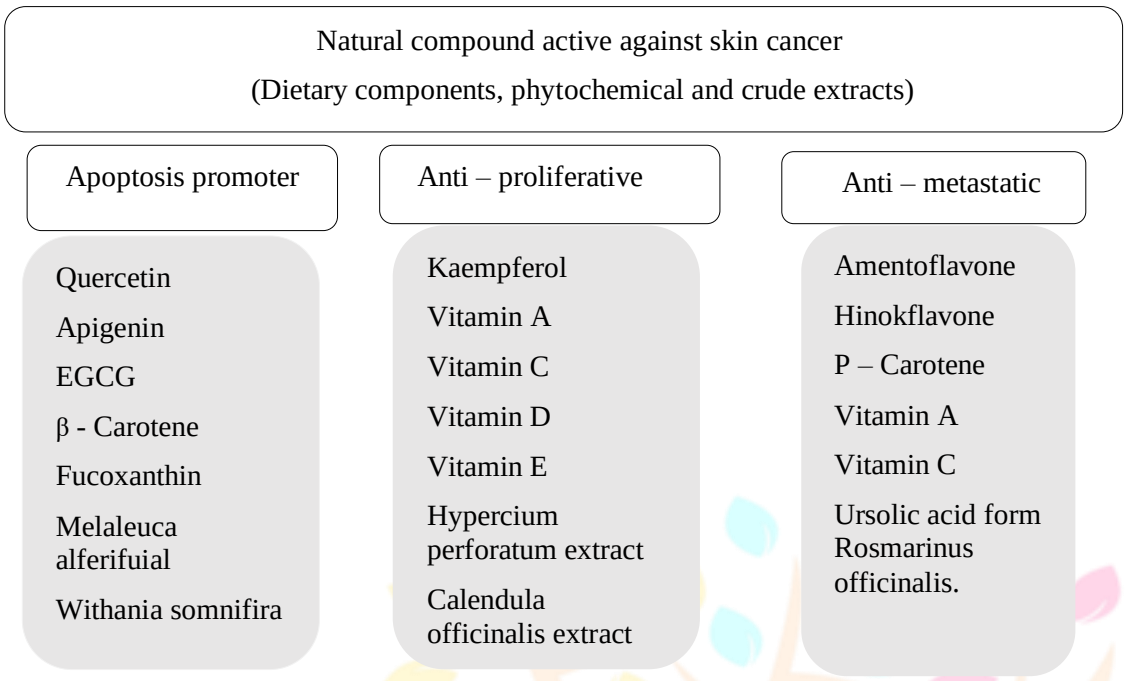
Fig. 1: Melanoma

SOURCES OF ANTI-CANCER COMPOUNDS IN NATURE

There is an abundance of unexplored resources of nature with medical potential throughout the world. More than half of the drugs available today have their origins in nature, and a significant proportion—over 70%—of Natural sources such as plants, animals, microorganisms, and marine species provide anti-cancer compounds.

Plants are the most widely used natural resource in pharmaceutical research among these. They are an important source for the discovery of novel medicines and lead compounds due to their abundance and accessibility. But even with the wide range of naturally derived medications, there are currently very few available that address malignancies of the skin. Notably, none have been approved for topical use, possibly as a result of the recognized adverse effects that these medicines have when administered topically.

In the sections that follow, we'll give you a thorough rundown of substances that come from a variety of natural sources and have shown promise in treating various cancers, with a focus on how well they might work against melanoma.



PLANT SOURCE:

More than half of the medications that are currently being used in clinical settings throughout the world have their roots in chemicals that were derived from plants. To facilitate the search for plant-derived anti-cancer drugs, the National Cancer Institute (NCI) in the United States of America began a plant collection program in 1960 and continued it until 1982.While this program led to the discovery of numerous cytotoxic agents from plant extracts, only a limited subset of these managed to progress to clinical use. Over a challenging two-decade period, taxanes and camptothecins underwent extensive development as pharmaceuticals for therapeutic use.

The pioneering emergence of vinca alkaloids, which include vincristine, vinblastine, and vinorelbine, constituted a noteworthy achievement as the first anti-cancer drugs produced from plants to be given clinical approval. Following these discoveries and approvals, derivatives of podophyllotoxin (e.g., teniposide and etoposide), taxanes (e.g., paclitaxel and docetaxel), and camptothecins (e.g., irinotecan and topotecan) were discovered. Mechanistically, Vinca alkaloids work with tubulin to interfere with the construction of the mitotic spindle, which causes actively dividing cells to die. In contrast, by stabilizing the microtubule, on the other hand, taxanes cause an imbalance between tubulin and microtubules, which disrupts regular cellular activity and ultimately results in cell death. Through different methods, camptothecins and podophyllotoxin inhibit topoisomerase I, which disrupts the process of cell division.

One noteworthy plant currently under investigation for its potential in treating various cancers, Viscum album L includes breast cancer, metastatic colorectal cancer, non-small cell lung cancer, and advanced pancreatic cancer. Positively, research on the combination of gemcitabine and Viscum album L. whole extract have shown comparatively high tolerability. Another compelling avenue of exploration involves a phase II clinical trial utilizing Polyphenol E, a green tea extract, for the treatment of chronic lymphocytic leukemia, with reported effectiveness and good tolerability. Additionally, when doxorubicin was combined with bebeerine, a naturally occurring is quinolone alkaloid, it showed encouraging effects in both vitro and in vivo tumor growth suppression in human melanoma cells and mice. Furthermore, when tested against skin cancer cell lines, extracts from Talia amurensis and Camellia sinensis were found to have cytotoxic effects in vitro. Ongoing investigations also highlight research into the potential applications of some phytochemicals has expanded because to their demonstrated heightened propensity for cytotoxicity towards melanoma and epidermoid carcinoma cells as compared to normal cells. These phytochemicals include Apigenin and epigallocatechin-3gallate.

ANTI-CANCER PHYTOCHEMICALS AND DIETARY INGREDIENTS

Phytochemicals renowned for their anti-inflammatory, immune-modulatory, and antioxidant properties are acknowledged for their significant potential in manifesting chemo preventive effects, especially concerning skin cancers Substantial endeavors have been invested in establishing a link between the phytochemicals' anticancer effects and antioxidant qualities. Nevertheless, tangible evidence of such a correlation remains elusive, the antioxidant activity of a phytochemical is increasingly considered a predictor of possible anticancer efficacy.

Within the myriad groups of phytochemicals, carotenoids, flavonoids, and terpenoids emerge as particularly promising candidates with notable anticancer potential. These compounds, sourced from diverse natural origins, have garnered research attention due to their versatile properties, encompassing anti-inflammatory, immune-modulatory, and antioxidant attributes. The exploration of these phytochemicals is propelled by the recognition that their distinctive combination of biological activities holds the potential to impede the initiation and progression of skin cancers.

Carotenoids, distinguished for their vibrant pigments found in fruits and vegetables, have exhibited antioxidant properties that could play a role in neutralizing free radicals, potentially hindering processes linked to cancer development. Widely distributed in plant-based foods, flavonoids showcase anti-inflammatory effects and have been implicated in the modulation of immune responses. Additionally, terpenoids, abundant in various plant species, possess antioxidant capabilities that contribute to their potential in anticancer activity.

While the precise mechanisms through which these phytochemicals exert their chemo preventive effects are intricate and multifaceted, the overarching consensus suggests that their collective anti-inflammatory, immune-modulatory, and antioxidant properties contribute significantly to their potential in impeding the onset and progression of skin cancers. Ongoing research endeavors aim to unravel the precise molecular pathways and interactions underlying the chemo preventive actions of these phytochemicals, paving the way for the development of innovative strategies in skin cancer prevention and treatment.

Flavonoids:

Flavonoids, derived from plant and flower pigments, are acetogenins. Their chemical structures are distinguished by two benzene rings connected through a linear carbon chain, along with an aromatic chromophore. The vibrant colors observed in plant parts rich in flavonoids are a result of the aromatic chromophore. Flavonoids are categorized into main groups such as flavonols, flavanones, flavones, isoflavones, flavan-3-ols (catechins), and anthocyanin's.

Flavonoids are widely recognized for their antioxidant properties, which involve scavenging free radicals, and their ability to chelate metal ions. Ongoing research continually explores their potential applications in disease treatment. The antioxidant activity of flavonoids can play a dual role in tumor genesis, either triggering or inhibiting the process, depending on various physiological factors. It's important to note that not all flavonoids may be beneficial for cancer chemotherapy or chemoprevention.

Certain flavonoids have demonstrated the ability to absorb ultraviolet B (UVB) rays, contributing to their photo protective effects in plants. They act as UV filters, safeguarding underlying elements. This photo protective property of flavonoids has been investigated in human cells and mouse models to explore the potential use of flavonoids and their derivatives as photo protective agents for humans.

Quercetin:

Quercetin, a flavonol distinguished by hydroxyl groups at positions 3, 5, 7, 3', and 4' in its structure, is soluble in alcohol, soluble in hot water, and mildly soluble in cold water. It stands out for its notable biological activities, primarily attributed to its antioxidant and anti-inflammatory properties, making it one of the most effective flavonoids. However, ongoing research is essential to determine the precise mechanisms by which quercetin carries out its antiancer actions; more research is necessary.

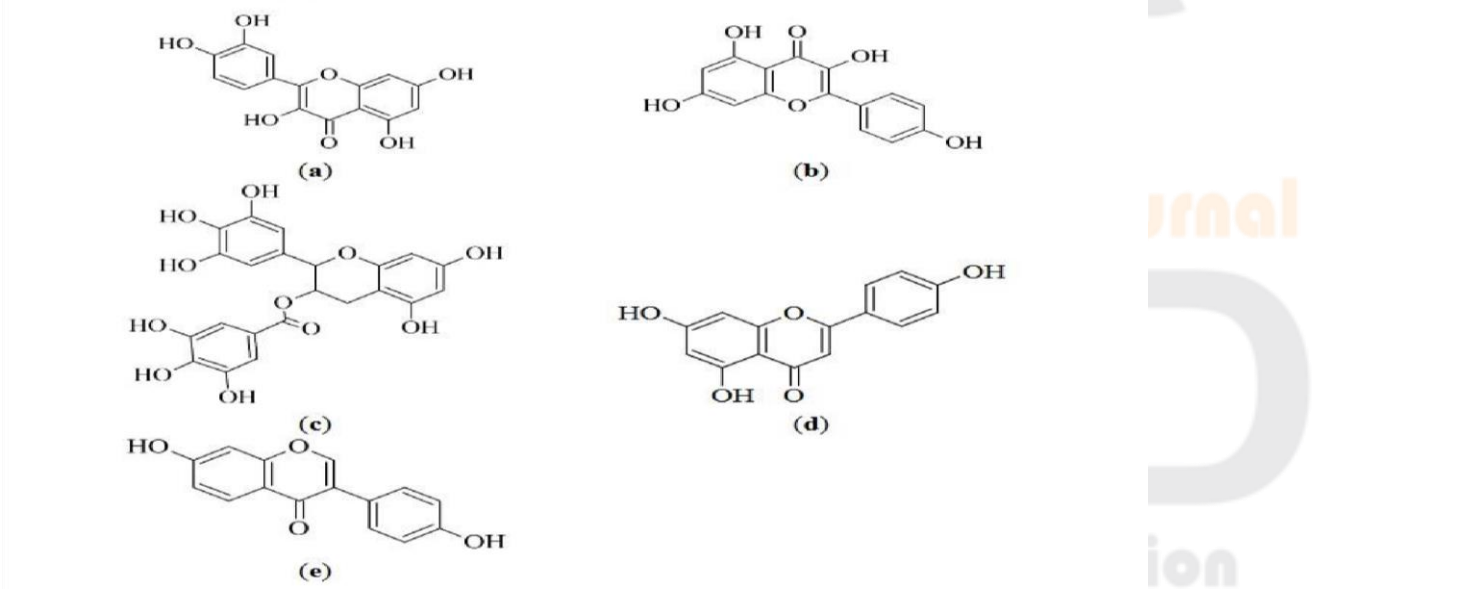


Figure.2 chemical structure of selected flavonoid possessing anti-cancer potential (a) Quercetin, (b) Kaempferol, (c) EGCG, (d) Apigenin, (e) Daidizein.

Abundant in the human diet, Quercetin is found in various glycosides forms in plants like apples, tomatoes, tea, grapes, Ginkgo, and St John's Wort. Onions, dark chocolate, capers, cloves, black elderberries, and oregano are also sources of Quercetin.

Studies have explored whether foods containing Quercetin offer protective properties against cancer. Quercetin has demonstrated anti-metastatic and chemo protective properties. By influencing cell viability and triggering apoptosis, it combats melanoma. Various mechanisms, such as influencing gene expression, potentiating caspase-3 activity, and inhibiting phosphoinositide-3 kinase (PI3-K), contribute to its anti-cancer effects. Recent findings suggest that Quercetin prevents UVB-induced DNA damage, oxidative stress, and apoptosis in mouse epidermal cells, inhibiting reactive oxygen species (ROS) generation and restoring antioxidant enzyme expression.

Topical formulations containing Quercetin have shown promise in inhibiting skin damage associated with UVB irradiation in mice. Nonionic and anionic formulations demonstrated inhibition of a decrease in glutathione and myeloperoxidase function, indicators of UVBinduced skin damage. Quercetin glycosides and polymethoxylate derivatives are thought to be ideal candidates for topical administration, and in vitro studies on nanoparticle formulations have demonstrated their efficacy in delivering drugs to the skin.

Kaempferol

Kaempferol, a widely abundant flavonoid in various foods such as tea, strawberries, green chili, carrots, pumpkins, and more, has sparked interest due to its medicinal properties. Despite being poorly water-soluble, it is found in significant amounts in numerous food items. Kaempferol chemical structure is depicted in Figure 2b. Epidemiological studies suggest a positive correlation foods high in Kaempferol and a decline in the prevalence of heart disease and several types of cancer, including pancreatic, ovarian, stomach, and lung cancer.

It is thought that Kaempferol works against cancer via promoting apoptosis and inhibiting cell growth, among other modes of action. Studies indicate its ability to block G2/M phase of the cell cycle development of choroidal melanoma. Application through the skin studies with systems of submicron emulsions demonstrated that the choice of the vehicle significantly influences flux, skin deposition, and lag time for Kaempferol. Skin permeation studies in albino mice revealed that Kaempferol in solution could effectively penetrate the skin barrier. Additionally, investigations into its antioxidant and cellular membrane protective effects have yielded promising outcome.

Epigallocatechin-3-gallate

Epigallocatechin-3-gallate (EGCG), depicted in Figure 2c, belongs to the flavan-3-ols group, known for its stability and water solubility. It is frequently present in red wine, green tea, strawberries, and cocoa-based products, with green tea being one of the main sources. Geographical data suggests that populations with high green tea consumption, like certain Japanese and Chinese groups, may have a lower incidence of prostate cancer.

When combined with vorinostat, EGCG has been shown to have promising anti-cancer effects by causing apoptosis and cell cycle arrest in melanoma cells. Synergistic anti-proliferative effects have been observed using EGCG and interferon in combination against mouse melanoma models in vivo and human melanoma cells in vitro. The caspases are activated, tumor suppressor proteins are induced, and proteins linked to apoptosis are regulated. EGCG's anti-skin cancer effects extend to its impact on suppressed tumor suppressor genes, which in turn caused skin cancer cells to express these repressed tumor suppressor genes through a decrease in DNA methylation. Notably, normal melanocytes are spared, as EGCG selectively activates the pro-apoptotic pathway in melanoma cells.

While EGCG holds promise as an anti-carcinogenic agent, it is also considered a potential photo protectant. Research suggests that it can stop photo damage, which is one of the main causes of skin cancer. Topical application of EGCG has shown a reduction in the formation of sunburn cells in rat skin exposed to UVA radiation, emphasizing its potential in skin cancer prevention.

Apigenin

Apigenin, a flavone with the chemical name 4', 5, 7-trihydroxyflavone (Figure 2d), is frequently found in onions, celery, oranges, tea, parsley, and thyme. It crystallizes as yellow, needle-like crystals. This bioactive flavone has garnered attention due to epidemiological observations linking flavone-rich diets to a reduced risk of certain cancers.

In vitro studies have demonstrated the anti-cancer properties of Apigenin in a variety of cell lines, such as liver cells, melanoma, and head and neck squamous cell carcinoma. One of its methods of action is to induce G2/M phase cell cycle arrest. Up regulating apoptotic pathways, down regulating anti-apoptotic proteins, and activating caspase-3, collectively resulting in its chemo-protective effects.

Apigenin exhibits that by preventing cell survival and proliferation, UVB radiation has protective effects on human keratinocytes grown in vitro and on mouse skin tissue grown in vivo through the NF-κB and MAPK pathways. Additionally, Apigenin inhibits the oncogenic kinase Src, leading to a reduction in cyclooxygenase 2 (COX-2) induced by UVB, reducing the inflammatory and carcinogenic consequences linked to COX-2.

Research on formulation has demonstrated that ethosomes and Nano-encapsulation enhance the skin deposition and apoptotic effects of Apigenin. When applied topically, Nano-encapsulated Apigenin has been shown to suppress the growth of tumors in mice exposed to ultraviolet B radiation, while in these mice, Apigenin administered orally in addition to being topically demonstrated to be a more effective inhibitor of carcinogenesis.

Daidizein

One soy isoflavones is Daidizein, whose chemical structure is depicted in Figure 2e. It belongs to the class of compounds known as phytoestrogens and is very soluble in situations that are alkaline. Studies have indicated its potential chemo-protective effects on the skin, as topical Daidizein application demonstrated effective photo protection. In vitro investigations revealed its ability to prevent cells from producing hydrogen peroxide as a result of UVB exposure, providing defense for keratinocytes. Genistein and daizéin, another isoflavones, have been investigated in a number of studies as synergistic cytotoxic agents, demonstrating encouraging cooperative effects. However, tape-stripping and Franz cell-based in vitro diffusion tests showed negligible penetration of Daidizein through the skin, limiting its exploration as an external chemo- and photo protectant.

Bioflavonoids:

Investigating the potential medical benefits of bioflavonoids has gained popularity in recent years. The ability of benevonoids, dimers of flavones, flavonols, and flavanones, to prevent melanogenesis has been established. Examples of compounds Amentoflavone, podocarpusflavone, volkensiflavone, fukugetin, and Hinokflavone are among the members of this category. Among these, Amentoflavone and Hinokflavone have been investigated for their ant melanoma activity.

Amentoflavone, which is extracted from Biorhythm sensitive, has been shown by Guruvayoorappan and Kuttan to inhibit tumor invasion, migration, proliferation, and angiogenesis, hence preventing B16F10 melanoma cells from metastasizing in vivo. Extracellular signal-regulated kinase (ERK), vascular endothelial growth factor (VEGF), and matrix metalloproteinase (MMPs) are thought to be modulated in relation to these effects. Additionally, Amentoflavone has been shown to have inhibitory effects on angiogenesis and endothelial cell migration that are connected to placental growth factor 1 (PlGF-1). Additionally, it has been observed that Amentoflavone prolongs the longevity of mice with metastatic tumors.

Using pharmacophore modeling, the possible MMP-9 inhibitory activity of Hinokflavone was examined, revealing its inhibitory effects on MMP-9 and suggesting ant metastatic effects [rephrase to avoid repetition.

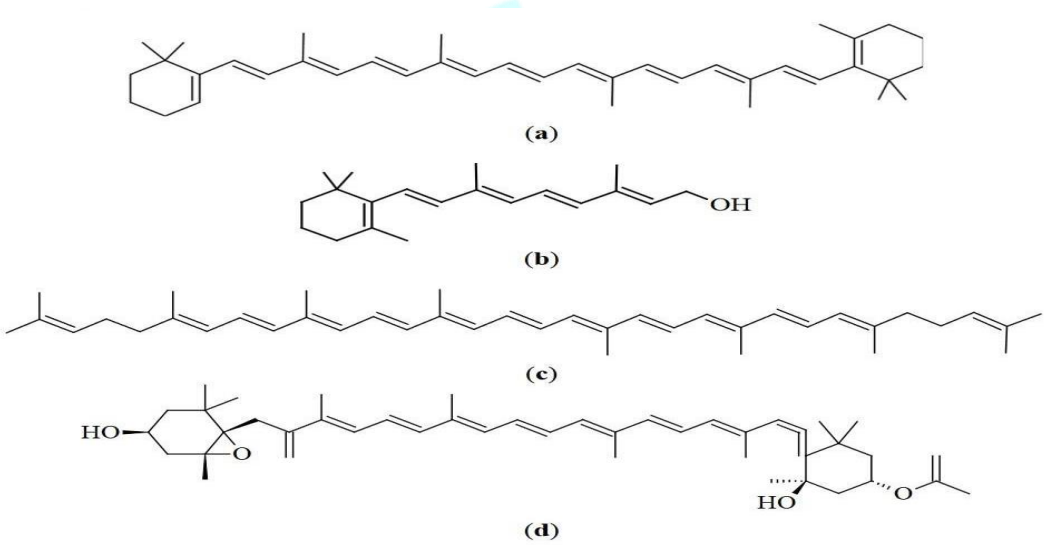


Figure.3 chemical structure of selected carotenoids: (a) β - carotenoids, (b) Retinol, (c) lycopene, (d) Fucoxanthin.

Vitamins

Carotenoids:

Naturally occurring pigments that dissolve fat and are abundantly found in nature, especially in plants, are called carotenoids. Composed of eight C5 isoprenoids forming C40 tetraterpenoids, carotenoids exhibit diverse chemical modifications (such as Functions of hydrogenation, isomerization, dehydrogenation, and oxygen presence), resulting in various carotenoid structures. The unique conjugated double bond system in carotenoids serves as a light absorbing chromophore, contributing to the vibrant colors of tomatoes, dark green vegetables, oranges, and other colorful foods can be described as yellow, orange, or red. (Figure 3a–d) provides visual representations of the chemical structures of discussed carotenoids.

Carotenoids are broadly classified into two primary categories: carotenes, which are very fat-soluble hydrocarbons, and xanthophylls, which are oxygen-containing, moderately polar carotenoids.

Pro-vitamin A carotenoids, exemplified by β-carotene, possess a substituted β ring and act as precursors to retinol in the body, playing a crucial role in vitamin A synthesis. Although nature boasts over 500 carotenoids, β-carotene, αcarotene, lycopene, lutein, astaxanthin, Fucoxanthin, and canthaxanthin are among the often researched ones.

Carotenoids, extensively researched for their medicinal properties, are considered possible preventative measures for diabetes, cardiovascular disease, and cancer. Their purported therapeutic advantages originate from antioxidant properties that lessen DNA damage brought on by free radicals, especially following UV radiation exposure. Carotenoids rich in pro-vitamin A are converted to retinol, exerting essential effects on cell proliferation, maintenance, and differentiation within epithelial tissues.

Vitamin C

Epidemiological studies on vitamin C and melanoma risk showed no preventive benefits; in likelihood of melanoma. None the less, research conducted both in vivo and in vitro showed that vitamin C effectively halted melanoma cell growth and induced apoptosis. Contrary to its antioxidant reputation, vitamin C's anti-cancer activity in melanoma is associated with oxidative stress via the caspases 8 route. Low ascorbate concentrations lead to melanoma cell death, while higher concentrations show a proliferative effect. Vitamin C up regulates p53

and p21, inducing cell cycle arrest. It also suppresses VEGF expression, inhibiting angiogenesis, and down regulates IGF-1R and COX-2, resulting in anti-proliferative effects.

Vitamin D

Vitamin D, obtained through sun exposure and various dietary sources, plays crucial functions in bone formation, immune system function, and cell proliferation. Although there was no correlation between vitamin D intake and the incidence of melanoma in epidemiological studies, there was a direct correlation with no melanoma skin cancers in women. In Italy, consumption of vitamin D was linked to possible advantages in terms of melanoma risk. Decreased skin tumors' expression of vitamin D receptors progress suggests a role in cancer progression. Vitamin D's anti-carcinogenic actions include reducing keratinocyte proliferation, enhancing differentiation, participating in the repair of DNA damage and the control of carcinogenic and malignant-suppressive long RNAs without coding. Paradoxically, excessive UVB exposure is linked to skin cancer, but moderate sun exposure, leading to vitamin D production, is thought to provide cancer-prevention benefits.

Vitamin E:

Nuts, seeds, vegetable oils, and whole grains all contain vitamin E, an antioxidant that is soluble in fat. The vitamin E family includes tocopherols and tocotrienols, with α-tocopherols being the most active. Studies on murine melanoma cells showed that α-tocopherols inhibits cell growth and proliferation through the COX pathway. Vitamin E supplementation increased cyclic AMP and prostaglandin E2 levels, inhibiting cell growth. In vivo, vitamin E succinate suppressed melanoma tumor growth and angiogenesis, inducing apoptosis. Formulations with tocopherols and tocotrienols demonstrated photo-protective effects. While topical vitamin E alone increased tumor burden in mice, a combination with vitamin C (CE Ferulic®) reduced tumor burden, suggesting effectiveness in late-stage tumor genesis. Nano formulations of vitamin E, in conjunction with other medications for the treatment of cancer, are under investigation.

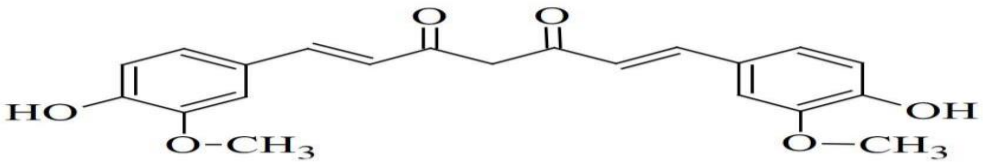
Terpenoids

Terpenoids, also known as terpenes or isoprenoids, are compounds found in various plants and have diverse applications, including medicines. Extracts from plants like Ferula spp, Ganoderma lucidum, and Coriolus versicolor containing terpenoids showed cytotoxic action in vitro on melanoma cells. Ganoderma lucidum extracts demonstrated anti-melanoma activity via apoptosis, oxidative stress, and suppression of cell division. Methanol extract from Coriolus versicolor decreased the growth and volume of tumors in melanoma cells by inhibiting proliferation and inducing apoptotic and necrotic cell death. Monoterpenes from Ferula ovine exhibited strong cytotoxic effect on melanoma. The terpenoid β-damascenone showed in vivo photo-protective effects against UV light exposure. Tea tree oil, rich in terpenoids, demonstrated anti-cancer activity against skin cancers, squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and actinic keratosis, among others, making it a potential candidate for further investigation in the treatment of skin cancer.

Curcumin:

Curcumin, a yellow plant polyphenol derived from turmeric, or Curcuma longa, is well-known for its antioxidant and anti-inflammatory qualities. While it has not received official approval for treating any disease, Curcumin has shown efficacy in various conditions, including epilepsy, cancer, HIV, diabetes, psoriasis. Curcumin, which makes up around 80% of commercial-grade turmeric, is being studied for its potential to reduce cancer symptoms like pain, depression, exhaustion, and by causing melanoma cells to undergo apoptosis and the opening of the mitochondrial permeability transition pore, Curcumin demonstrates anti-melanoma action. It functions without the involvement of p53, suppresses the pro-survival NF-κB pathway, and initiates the apoptotic pathway launched by Fas. Topical Curcumin application delayed UVB-induced carcinogenesis in mice, reducing tumor appearance and volume without toxicity. Oral Curcumin administration down regulated anti-apoptotic Bcl-2 and PCNA in melanoma tumors. It also inhibited squamous cell carcinoma growth through ribosomal S6 phosphorylation inhibition. Challenges in curcuma's use include low solubility and bioavailability, prompting research on Nano formulations like liposomes and micro emulsions for enhanced delivery. Propylene glycol liposomes and a limonene-based micro emulsion show promise as Curcumin delivery vehicles. Dual drug-loaded Nano particulate formulations, such as curcumin-piperine, aim to address resistance, solubility, and bioavailability concerns in anti-melanoma therapy.

Sulforap



Known f uch as cauliflower, broccoli, cabbage, radish, and kale. Studies on melanoma cells have reported its effectiveness in inducing apoptosis, inhibiting stopping metastasis and promoting cell growth.

Sulforaphane induces apoptosis in melanoma cells by up regulating caspase 9, caspase 3, p53 protein, and the Bax gene while down regulating Bcl-2, Bid, and caspase 8. Sulforaphane anti-metastatic qualities and potential for use in cancer immunotherapy through immune response factor modulation are demonstrated by in vivo experiments on a mouse melanoma model. However, sulforaphane faces challenges such as instability at high temperatures, a brief half-life combined with poor absorption. Research on drug delivery systems, including albumin

microspheres and magnetic microspheres, has demonstrated enhanced and long-lasting suppression of tumor development in contrast to sulforaphane solution.

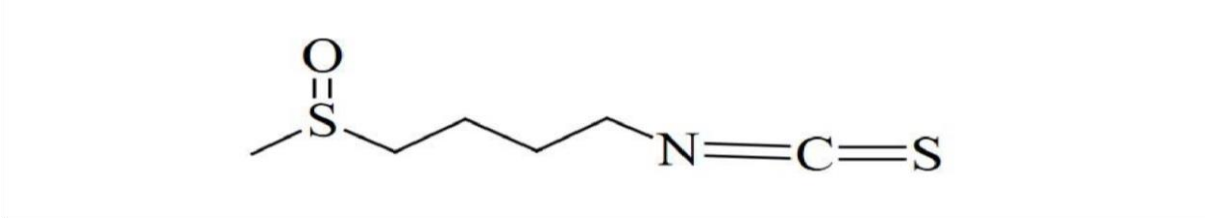


Figure 5. Chemical structure of sulforaphane

CRUDE PLANT EXTRACT'S ANTI-MELANOMAS:

Hypercium perforatum

St. John's Wort contains hypericin, a photo-sensitizing chemical with concentration- and light-dependent effects that can be used in photodynamic therapy (PDT) to treat skin malignancies. Research shows that UVA-induced hypericin activation results in necrosis and apoptosis in melanoma cells. Although hypericin has demonstrated potential, therapeutically used aminolevulinic acid methyl ester is thought to have better photo-sensitizing properties, possibly due to hypericin's low solubility and stability issues. Hydro-alcoholic and polar methanolic extracts of St. John's Wort have demonstrated inhibitory effects on melanoma cells, making them potential candidates for further investigation as PDT photosensitizers in skin cancer therapy.

Withania somnifera

Withania somnifera, often known as ashwaghanda or Indian ginseng, is a plant in the Solanaceae family that is the primary source of a class of powerful medicinal chemicals known as withanolides. An ant proliferative impact was seen when native and derivative withanolides were applied to two melanoma cell lines. Withaferin a (WA), the most potent and extensively researched withanolides, has been suggested to have potential for treating melanoma patients who are hyperthermic. During the course of treating hyperthermia, Withaferin A was found to boost the tumor response and lower the degree of thermo-tolerance Given that radiation alone did not produce the same therapeutic outcome in a murine model, a combination of radiation, hyperthermia treatment, and a non-toxic dose of WA has been proposed as a potential alternative for melanoma therapy. Melanoma cells undergo apoptosis when Withaferin A alone acts as an initiator. While a methanolic extract of Withania somnifera has been demonstrated to suppress metastasis in a mouse melanoma model, it also produces ROS and down regulates Bcl-2.

Melaleuca alternifolia

Melaleuca alternifolia is the source of tea tree oil, which is widely recognized for its numerous therapeutic benefits, particularly in relation to skin conditions. Research has been done on terpinen-4-ol, the primary active ingredient of M. alternifolia, and its anti-cancer properties. At dosages that are not harmful to normal fibroblast cells, terpinen-4-ol and tea tree oil have been shown to suppress melanoma cell development in vitro by inducing cell cycle arrest, apoptosis, necrosis, and reduction of cell proliferation. The results of topical application In 2014, molecules containing 10% tea tree oil in dimethyl sulphoxide were administered subcutaneously to mice harboring melanoma tumors. The results of the investigation revealed a noteworthy reduction in tumor growth .Melanoma cell and tumor growth has been shown to be inhibited both in vitro and in vivo by M. alternifolia oil and its terpenes components.

Zingiber officinale

The monocotyledonous herb ginger (Zingiber officinale) grows as a rhizome. The anti-cancer potential of 6-gingerol, an active ingredient of Zingiber officinale, has been studied in melanoma and epidermoid carcinoma cells (SCC). 6-Gingerol did not directly affect the melanoma cells, but it potently reduced the angiogenesis generated by VEGF. According to reports, 6-gingerol inhibits proliferation and induces apoptosis in epidermoid carcinoma cells. It also has anti-proliferative properties. ROS appear to control the apoptotic process. These results indicate that 6-gingerol reduces the growth of melanoma tumors by altering the tumor's venous supply; nevertheless, in SCC, it can cause cell death through apoptosis.

Viscum album

Mistletoe (Viscum album) contains anti-cancer and immunostimulatory properties that have shown promise in enhancing the quality of life for cancer patients. European mistletoe, particularly its lectins, has been extensively studied, while Korean mistletoe has reported preventive and therapeutic inhibitors of metastasis, thought to entail activation of macrophages and natural killer cells. Anti-angiogenic properties contributes to the antimetastatic effects of mistletoe from Korea. Lectins from European mistletoe induce apoptosis affects human melanoma cells and, via immune-modulatory mechanisms, stop the formation of tumors in mice. A terpenes extract containing oleanolic- and betulinic acid induces apoptosis and necrosis in melanoma cells. Subcutaneous mistletoe therapy in patients with primary malignant melanoma and a case study of metastatic malignant melanoma suggest potential survival benefits and complete remission, respectively.

Calendula officinalis

Calendula officinalis (C. officinalis) flower extracts are widely recognized for their anti-inflammatory and anti-cancer qualities. A laser-activated extract of C. officinalis has been shown by Jimenez-Medina et al. To suppress tumor cell proliferation in human cells as well as cell growth in murine melanoma cells. Potent cytotoxicity against melanoma was demonstrated by certain triterpene glycosides from C. officinalis extract; more research on these chemicals alone or in combination is advised Molecules 2014, 19 11702. According to reports, marigold has a highly specific anti-cancer activity against human melanoma Fem-x cells, with 50% inhibitory concentration (IC50) values of 0.36 ± 0.12 mg/mL, compared to 0.75 ± 0.21 mg/mL for HeLa cells and 2.30 ± 0.08 mg/mL for human colon carcinoma cells. With an IC50 value above 16.67 mg/mL, marigold tea demonstrated a greater anti-melanoma effect than chamomile (Matric aria chamomilla) tea. Additionally, C. officinalis extract taken orally demonstrated anti-metastatic properties that extended the life span of mice with metastatic tumors.

Rosmarinus officinalis:

Rosemary (Rosmarinus officinalis) contains phenolic diterpenes and triterpene, including carnosol and Ursolic acid, known for their antioxidant properties. Carnosol inhibits migration of metastatic melanoma cells by suppressing MMP-9, also reducing cell viability and growth at higher concentrations. Ursolic acid stimulates p53 expression and inhibits NF-κB, inducing apoptosis in melanoma cells. It enhances apoptosis during radiotherapy, suggesting potential adjuvant use in melanoma treatment. Ursolic acid's anti-angiogenic effects involve inhibiting VEGF, MMP-2, MMP-9, and nitric oxide production. These findings highlight the therapeutic potential of rosemary compounds in combating melanoma.

***Aloe* species:**

Aloe, renowned for its medicinal properties, including wound healing and skin treatment, has shown potential against melanoma. Saline extracts of Aloe Vera reduced murine melanoma viability of cells in a concentration-dependent way. Emodin, a functional ingredient, demonstrated time-dependent anti-proliferation, MMP-9 inhibition, and anti-metastatic activities. Melanoma cell adhesion, migration, invasion, and aggregation were all inhibited by aloe-Emodin. In a studyAloe-emodin exhibited cyto-protective properties in the presence of cytotoxic chemicals, accelerated cell differentiation, and inhibited the development of human and murine melanoma cells. Another Aloe compound, aloin, slowed down the proliferation of melanoma cells considerably, interfered with cell adhesion, and made the cancer more susceptible to the deadly drug cisplatin.

Artemisia* Species*:

The genus Artemisia has more than 500 distinct species of fragrant plants and shrubs. In human melanoma cells, euphemilin, a flavonoid derived from the Artemisia species, has been demonstrated to reduce cell growth, induce apoptosis, and cause G2/M cell cycle arrest. Ludartin from A. amygdaline (almond wormwood), dehydroleucodine, and dehydroparishin-B from A. douglasiana (California Mugwort) are other previously investigated artemisin derived chemicals. It has been discovered that dehydroleucodine and dehydroparishin-B impede cell migration and limit cell proliferation in murine melanoma. Additionally, Ludartin has been shown to exhibit cytotoxic activity against mouse melanoma cells (IC50 of 6.6 μM) and human epidermoid carcinoma cells (IC50 of 19.0 μM). The cytotoxic activity of Artemisia essential oils has also been studied, in addition to specific components. When examined for cytotoxic effect against melanoma, essential oils isolated from the varied wormwood herb A. anomala were shown to have an IC50 value of 0.2 μL of oil per milliliter.

***Alpinia* Species:**

There has been research done on the potential anti-cancer properties of extracts from several Alpine species. Particularly, the potential anti-melanoma properties of extracts from A. oxyphylla (sharp leaf galangal), A. galangal (larger galangal), and A. officinarum (lesser galangal) have been investigated. It was discovered that an extract of A. oxyphylla from supercritical fluid carbon dioxide inhibited the growth of human melanoma cells. It has been observed that two substances isolated from A. galangal, namely 1, 7-bis (4-hydroxyphenyl)-1, 4, 6-heptatrien-3-one and bisdemethoxycurcumin, markedly reduced the growth of melanoma cells. A. officinarum galangin molecule inhibited cell division and triggered apoptosis via activating p38 MAPK and the mitochondrial pathway. Galangin was also found to have suppressed lamellipodia formation, motility, adhesion, and spreading of cells in vitro in another investigation. In a mouse melanoma model, it was shown that galangin prevented lung metastases in vivo.

CONCLUSION*:*

This review underscores the potential of naturally derived compounds in future melanoma treatments, summarizing studies on various compounds and plants with potential anti-cancer properties. Phytochemicals, offering health benefits, are subjects of ongoing research, with anti-cancer effects often attributed to specific compounds or their combinations in crude extracts. While in vitro studies show anti-cancer activity, clinical confirmation is necessary.

Although using natural substances to treat cancer is a cost-effective method, commercialization could put a burden on resources and raise concerns about quality. Safety concerns include toxicity and misidentification of plants. In order to optimize herbal products for safe human usage, scientific study is necessary. Some natural products may alleviate cancer symptoms or treatment side effects, leading to increased self-medication. However, caution is needed, as not all natural products are safe, and practitioners must be educated on their use.

Quality assessment of herbal therapies is challenging due to individual tailoring and lack of standardization. Large randomized trials are recommended to determine herbal medicine effectiveness. In an effort to deliver reliable information, the US National Institute of Health (NIH) funds research on complementary and alternative medicine (CAM) therapies. Healthcare professionals are urged to practice pharmacovigilance and ensure informed decisions regarding CAM. Online news sources are encouraged to report accurate information on CAM for public awareness.

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