Potential Phytochemicals and Dietary Components for the Prevention and Treatment of Skin Cancer: A Review

By

Habibatul Muntaha
16236006

A thesis submitted to the Department of Math and Natural Sciences in partial fulfillment
of the requirements for the degree of
Bachelor of Science in Biotechnology

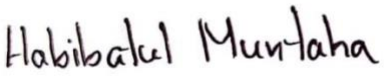
Department of Mathematics and Natural Sciences
BRAC University
Summer 2022

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

Student's Full Name & Signature:



Student Full Name
Student ID

Approval

The thesis/project titled "**Potential Phytochemicals and Dietary Components for the Prevention and Treatment of Skin Cancer: A Review**" submitted by Habibatul Muntaha bearing the ID: 16236006 of Summer 2022 has been accepted in partial fulfillment of the requirement for the degree of Bachelor of Science in Biotechnology.

Examining Committee:

Supervisor:

Rafeed Rahman Turjya
Lecturer, Department of Mathematics and Natural Sciences
BRAC University

Program Coordinator:

Iftekhar Bin Naser
Assistant Professor, Department of Mathematics and Natural Science
BRAC University

Departmental Head:

Prof. A. F. M. Yusuf Haider
Chairperson, Department of Mathematics and Natural Science
BRAC University

Acknowledgment

I would like to express my deepest appreciation to all those who provided me with the opportunity to complete this report. The accomplishment and completion of this report would not have been viable without the contribution of some accommodative people, who gave their valuable time from their busy schedule to guide me in doing these project work. I would like to extend my heartiest gratitude to all those who directly or indirectly contributed to the competition of the report.

At the beginning, I would like to convey my gratitude and appreciation to my honorable academic supervisor **Rafeed Rahman Turjya**, Lecturer, Department of Mathematics and Natural Sciences, BRAC University for providing valuable guidelines in preparing the report. I am deeply grateful to him for guidance, support, constant supervision, constructive criticism, and devoted involvement during this whole research period. Without his guidance it would not be possible for me to prepare this report.

I pass on the gratitude to **Dr. Iftekhar Bin Naser**, Assistant Professor and Coordinator, Biotechnology program, Department of Mathematics and Natural Sciences, BRAC University for motivating me and giving me the best advice, and guiding me throughout the whole process.

Furthermore, I would like to acknowledge with much appreciation the support of our **Professor A F M Yusuf Haider**, Chairperson of the MNS department, for allowing me to complete my undergraduate thesis smoothly.

Finally yet importantly, I would like to thank all my friends, family, and support staffs who have made this journey easier and better in different ways for me.

Habibatul Muntaha

16236006

Abstract

Cancer is a global health issue that takes the lives of at least one in every six people worldwide; it can originate in almost any tissue of the body, including skin. Skin, the largest human organ, protects us from all the harmful and toxic components of environment. Its exposure to the environmental stress events e.g. harmful chemicals, ultraviolet ray, and viruses can cause skin cancer, including both melanoma and nonmelanoma skin carcinoma. For skin cancer, currently there are a variety of conventional treatment options available, all of which have drawbacks such as toxicity, multidrug resistance, and high expenditure. On the other hand, the use of complementary alternative medicine (CAM) with the intervention of phytochemicals and natural products has showed less toxic effect in the treatment. This seems a more cost-efficient, effective, and safer method for preventing and treating cancer. Using these bioactive compounds in *in vitro* and *in vivo* testing for the treatment and prevention of malignant cell lines have shown their role in regulating tumor promoting proteins, carcinogenic factors, and signal pathways involved in cancer progression. These can help in promoting cell apoptosis, inhibiting cell proliferation, angiogenesis, and metastasis, sensitizing cancerous cells, and boosting the immune system. This review provides an overview of the potential phytochemicals (including flavonoids, carotenoids, vitamins, sulforaphane, and resveratrol) in cancer therapies, discussing their bioavailability, natural sources, molecular mechanisms of action, and therapeutic potentials.

Table of Contents

Declaration i

Approval ii

Acknowledgement iii

Abstract iv

Table of Contents v

List of Figures vii

List of Tables viii

Chapter 1: Introduction 1

Chapter 2: Types of Skin Cancer 4

2.1 Basal Cell Carcinoma 5

2.2 Squamous Cell Carcinoma 5

2.3 Melanoma 6

2.4 Merkel Cell carcinoma 7

Chapter 3: Current Diagnostic and Therapeutic Strategies of Skin Cancer 9

Chapter 4: Dietary and Phytochemical Compounds for the Treatment of Skin Cancer 11

4.1 Flavonoids 12

4.1.1 Apigenin 13

4.1.2 Kaempferol 15

4.1.3 Quercetin 16

4.1.4 Epigallocatechin 18

4.1.5 Daidzein **19**
4.2 Carotenoids **20**
4.2.1 Lycopene **22**
4.2.2 Fucoxanthin **23**
4.2.3 Curcumin **25**
4.2.4 β-carotene **27**
4.3 Vitamins **28**
4.3.1 Vitamin A **28**
4.3.2 Vitamin C **30**
4.3.3 Vitamin D **32**
4.4 Sulforaphane **34**
4.5 Resveratrol **36**
Chapter 5: Conclusion 37
Abbreviations 41
Bibliography 44

List of Figures

Figure No.	Caption	Page
Figure 2.1	A structure of skin layers including the part where skin cancer can occur	**4**
Figure 2.2	Normal merkel cells	**7**
Figure 4.1	Chemical structure of some of the flavonoids, (a) quercetin, (b) kaempferol, (c) EGCG, (d) apigenin and (e) daidzein	**13**
Figure 4.2	Chemical structures of some of the carotenoids: (a) βcarotene, (b) retinol, (c) lycopene and (d) fucoxanthin	**21**
Figure 4.3	Chemical structure of Curcumin	**25**
Figure 4.4	Chemical Structure of vitamin A	**28**
Figure 4.5	Chemical structure of vitamin C	**30**
Figure 4.6	Chemical structure of vitamin D	**33**
Figure 4.7	Chemical structure of sulforaphane	**35**
Figure 4.8	Chemical Structure of Resveratrol	**36**
Figure 5.1	Different phytochemicals are involved in regulating various molecular process to modulate skin cancer	**38**

List of Tables

Table No. Caption Page

Table 4.1 Active dietary components and phytochemicals against skin **11** cancer

Chapter 1

Introduction

Cancer is one of the leading causes of death worldwide, and since 2010, it has been second on the list. According to GLOBOCAN 2020, there were nearly 19.3 million new cases of cancer in 2020, and close to 10 million deaths [1-2]. Cancer mortality is higher in men than in women (189.5 per 100,000 men and 135.7 per 100,000 women). Based on data from 2016 to 2018 in the United Kingdom, those aged 90 and over has the highest mortality rate for all kind cancer and half of the cancers deaths in UK occur in people aged 75 and up each year.

Skin cancer is a disease that affects the cells that make up the skin on the human body. These cells begin to reproduce abnormally and eventually spread throughout the body via the lymphatic system. Skin cancer occurs the most in Australia, New Zealand, and The Netherlands, following the region, environment, race and color of people of these countries. According to statistics, over 9500 people are diagnosed with skin cancer every day, with two people dying every hour [3-4]. People who are older have a larger risk of dying from skin cancer than those who are younger. Each year, almost 7180 individuals die from cutaneous melanoma and 2000 people die from basal cell cancer, respectively. Additionally, 4630 people die every year from other less common types of cancers [6]. Melanoma and non-melanoma skin cancers are becoming more prevalent in the white population. Basal cell carcinoma and squamous cell carcinoma develops in children and adults due to intensive sun exposure. In addition, people are now diagnosed with merkel cell cancer more than ever before. Most of the merkel cell carcinoma cases (90%) are diagnosed in white people. Also, men and those over the age of 70 are the most likely to be diagnosed with merkel cell cancer [5, 7].

One of the leading causes of skin cancer is ultraviolet exposure. Aside from UV radiation, other causal agents for skin cancer include viruses, mutagens in foods, mutagens in chemicals, and genetic predisposition. Avoiding sun exposure, applying sunscreen, and managing and eliminating the causative agents can all help to prevent skin cancer. Treatment for skin cancer varies depending on the size, type, depth, and location of the

cancer [8-9]. Skin cancer that are only limited on the surface can be treated through initial skin biopsy, which in most of the cases removes the entire growth of cancer. For additional treatment skin care is treated by cryosurgery, excisional surgery, chemotherapy, cryotherapy, radiation therapy, photodynamic therapy, biological therapy etc. Also skin cancer can be effectively removed through anti-angiogenesis, which helps to reduce the tumor growth [10-11].

All these types of therapies have both advantages and disadvantages, but these therapies have severe side effects. For example, chemotherapy is a treatment which destroys all dividing cells by using chemical agents as it is nonspecific. The chemical agents directly interact with function of the cell and DNA synthesis to kill cancer cells. As a result, it causes side effects such as hair loss, nausea, vomiting, diarrhea, anemia, infections, exhaustion, taste bud loss, and immune system degradation. Another issue is the emergence of multiple medication resistance. Cancer cells grow resistant to medicines in some of the approaches, which is then sought to be overcome by a further treatment. However, in the vast majority of situations, these subsequent treatments are extremely harmful to the patient. Therefore, it is very hard to choose the right treatment for the patient considering patients health as well as type and situation of the cancer [12]. On account of the disadvantages of conventional cancer chemotherapies, for over past 15 years the use of Complementary and alternative medicine (CAM) has increased. CAM has some disadvantages due to its chemical composition, preparation method, and dosage determination as well as side effects like stomach aches, gastric upset, nausea, diarrhea, migraine etc. People who has experienced CAM, among them 4.4% have faced side effects, 3.2% have not benefited at all, but 22.4% people were benefited by increasing the ability to fight cancer and 42.5% found it helpful for improving emotional well-being.

Phytochemicals are physiologically active substances obtained from extracts of plant roots, leaves, stems, barks, bulbs, and other parts of plants that have substantial anticancer potential [12-13]. Phytochemicals help to stop the formation of carcinogens and from attacking the cells, as well it helps to wipe out the cancer cells. Though worldwide people have increased using CAM, because they believe that natural/herbal products are safer, that is not quite the case always. Researchers and scientists are working *in vivo* and *in vitro* to

make it side effect free, more effective for potential anticancer biological activity. This review provides an overview of natural products that can be used to treat and prevent skin cancer [13-14].

Chapter 2

Types of Skin Cancer

Skin cancer can occur to anyone, yet in accordance with the variety of geography and skin type, the risk of skin cancer in individuals varies; such as people of Australia, New Zealand, and United states are at higher risk [14]. When the healthy cells of our body which form skin cell start changing and dividing abnormally, it results in formation of a benign tumor. It can later become cancerous after metastasizing in other cells and tissues of the body. Usually skin cancers occur by excessive exposure to ultraviolet radiations from the sun, which may occur from thinning ozone layer, radiation etc. Apart from these viruses, carcinogens, harmful chemical agents etc. are also the reasons for skin cancer. Light skin and Caucasian people are at higher risk in catching skin cancer. Skin cancers are many types; among those non-melanoma skin cancer, basal cell carcinoma, merkel cell carcinoma, squamous cell carcinoma, melanoma skin cancer are the most common [15-17].

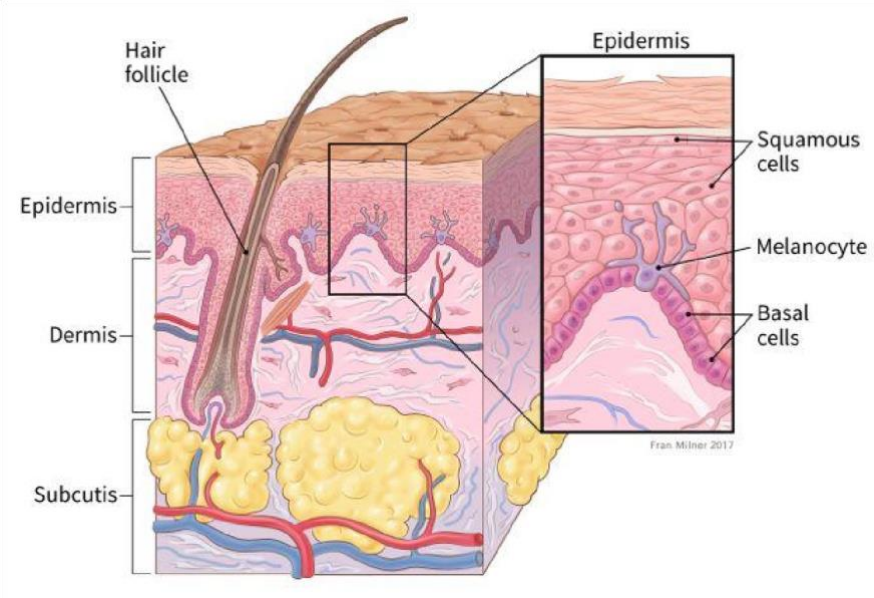


Figure 2.1 *A structure of skin layers including the part where skin cancer can occur (Adapted from [119])*

2.1 *Basal Cell Carcinoma*

One of the most common skin malignancies is basal cell carcinoma (BCC). Each year, BCC affects around 3.6 million people in America. BCC is found in the basal cells of the skin, which is in the lower part of the epidermis. Once it starts dividing abnormally, it continuously divides to form new cells, moves up in the epidermis, gets flatter, and eventually ends up replacing the squamous cell (Figure 2.1). BCC usually develops for heavy UV or sun exposure, but other than this ionization radiation, low intake of vitamin, chemical and dust exposure, immunosuppressive treatments, and high dietary energy like fat as well as exposure to arsenic carry a huge risk of BCC [18-19]. Additionally, genetic conditions like Gorlin's syndrome, Bazex's syndrome, albinism, xeroderma pigmentosa have an increasing risk for basal cell carcinoma. Since most of the BCC cases occur because of UV or sun exposure, most affected areas are face, head, and neck. Open sores, pink growths, red patches, scars with slightly rolled borders, shiny lumps, and a center indentation are the primary signs of BCC, with time which can form crusts, itching, ooze and bleeding. BCC usually grows slowly, so it has a rare chance of spreading to the body's other parts. However, if it is not medicated in the beginning or left untreated, then it metastasizes in others tissues and bone in the body [20].

2.2 *Squamous Cell Carcinoma*

After BCC, the second most common skin malignancy is squamous cell carcinoma (SCC), which is the leading cause of death by non-melanoma cancer around the world. Like BCC, people of the United States have a higher risk in SCC. It is found in the outer layer of epidermis, flat looking cells, called squamous cells. Usually these cells keep shedding continuously as the new ones form. But when the cells start growing abnormally, it becomes squamous cell cancer (Figure 2.1) [20-21].

SCC mostly occurs because of the exposure to UV radiation. UV radiation forms thymidine dimer in the tumor suppressor gene, which results in formation of tumor if the mutation is not repaired. Other than UV radiations, x-rays, gamma rays, ionizing radiation also causes

SCC. Additionally, genetic conditions like genodermatoses, occulocutaneous albinism, xeroderama pigmentosum, and chemical exposure like arsenic, polycyclic aromatic hydrocarbons carry a higher risk in SCC. Including these human papillomavirus (HPV) infection, immunosuppressive medications, organ transplants like renal or heart transplant patients have also a risk of squamous cell cancer [22]. Moreover, there are some precancerous skin conditions that can turn into SCC like Actinic keratosis, Keratoacanthoma, Bowen disease etc. Bowen disease is also called squamous cell cancer *in situ*, as it is actually an earlier form of squamous cell cancer.

SCC can appear anywhere on the body, including the oral and genital region. It takes shape like red patches, open sores, uneven, bumpy, thickened or wart-like skin, or swollen growths with a central depression, and with time it turns into crust which may itch or bleed. SCC can be treated successfully, but delaying in treatment or no treatment at all can make it dangerous and sometimes deadly as it can grow into the deeper layers of body and invade in other tissues and bones of the body [23].

2.3 *Melanoma*

Melanoma is one of the deadliest skin cancers. Three quarters of all skin cancers occurs because of melanoma and it causes premature death. Light skin people are at highest risk of being affected by melanoma [24]. Melanoma occurs in the melanocytes, pigmentproducing cells situated at lower parts of the epidermis (Figure 2.1). The dark, tan, brown skin color of human skin is caused by a dark, brown like pigment called melanin, which is produced in melanocytes. Melatonin functions as a shield for human skin, it saves the deeper layer of skin from damaging radiations of the Sun. When these melanocyte cells mutate and start dividing uncontrollably, then melanoma skin cancer occurs.

Like other skin cancers, melanoma is mostly formed from heavy exposure to sun and UV rays [23-24]. Mutation in a gene named *BRAF* is linked with melanoma. This gene produces a protein B-raf. Overexposure to ultraviolet rays causes mutation in this gene. And this mutated gene produces continuously unregulated B-raf kinase enzymes, as a result uncontrolled cell growth occurs, and this leads to the formation of melanoma cell cancer.

Other than BRAF, there are also some genes like *MC1R, CDKN2A,* where mutation can give rise to melanoma [25]. People with light skin, high number of moles, atypical mole, freckles, congenital melanocytic nevi (brown birthmark), pale skin, light eyes, red or light hair, immunodeficiency, older age, organ transplant, actinic lentigines have a higher risk of melanoma.

Skin changes like sudden changing shape, size, and color of any spot or mole, painful. Itchy, shiny, waxy, smooth, dry, scaly, crusty, rough red spot or sore or lumps that sometimes start to bleed are symptoms of melanoma. Melanoma can occur in any part of the body including parts like the eyes and intestine. It mostly occurs in men's chests and back and women's leg. As melanoma occurs because of the heavy sun exposure and sunburn, so avoiding sun, UV radiation, tanning bed can reduce the risk factors a lot, also people with higher melanin or darker skin has very lower risk for melanoma [26].

2.4 *Merkel Cell Carcinoma*

Merkel cell carcinoma (MCC) is an uncommon, severe form of cutaneous neoplasm that has a higher fatality rate. It metastasizes much faster than the other skin cancers. In a study, it was found that MCC each year affects about 3000 people in the United States, and it is anticipated that this number will increase to 3250 by year 2050 [27].

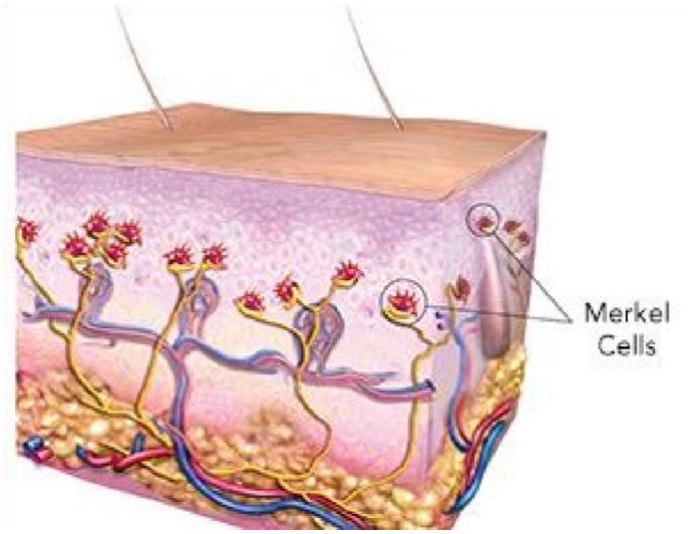


Figure 1.2 *Normal merkel cells (Adapted from [27])*

In mammals, merkel cells can be found as single cells or clusters in the epidermis of skin and in mucosa of the basal layer. These are 10-15μm long clear, oval shaped cells or clusters connected to a nerve receptor called mechanoreceptors; which work as touch sensors in our skin (Figure 2.2). There are some other merkel cells in our body which are connected to nerve terminals, but they do not function as mechanoreceptors. These merkel cells are part of the neuroendocrine system [28].

Merkel cell cancers are highly malignant. Like any other skin cancer, excessive exposure to sunlight and UV rays is the greatest risk factor for MCC. Besides, people with older age, previous sun-related skin conditions, history of other skin cancers like BCC, SCC, people who have autoimmune disease, who have weakened immune system like HIV, people who are on immunosuppressive agents for organ transplant, chemotherapy, radiotherapy, also on chemical exposure like arsenic, and people with light complexion have a high chance of being affected with MCC [29]. In 2008, researchers discovered a common virus called polyomavirus in the merkel cells of the skin. It has a double stranded, supercoiled DNA with oncogenic potential like viral replication and inactivation of tumor suppressor proteins p53 and pocket retinoblastoma. Some cases of MCPyV have been seen by scientists in different types of specimens of MCC. Since, merkel cell cancer is a rare disease to occur, and the virus is very familiar in the merkel cells, the scientists find it very likely that there must have been other risk factors than this virus to cause MCC [30].

MCC can develop in areas of the body, but mostly on the exposed areas. At first the tumor appears as painless, pimple-like lumps, in red, purple or bluish red color in the skin, because of its rapid growth and spreading it comes into the notice of patients and doctors very fast. Considering its fast metastasizing capacity, it is three to five times more deadly than other skin carcinomas. Early treatment can reduce MCC completely, but once the disease spreads the type of treatment is changed as it becomes harder to treat it completely [28-29].

Chapter 3

Current Diagnostic and Therapeutic Strategies of Skin Cancer

Skin malignancy can quickly be prevented if some necessary steps are taken. The bright (UV) beams of sun is the single most serious danger factor for creating skin malignant growth. The 3 main UV rays that the sun radiates are known as UVA, UVB and UVC. 95% of the UV radiation arriving at earth is UVA beams, which is a main reason for photo aging because of their capacity to enter into the skin [31]. UVA rays are known to prompt DNA damage by making free radicals of reactive oxygen species and diminishing the action of antigen-introducing cells of the epidermis. UVA rays are utilized in tanning stalls, and can enter mists and glass. UVB rays have a 290 to 320 nm frequency and are more connected with skin disease than UVA tanning beams, which have a 320 to 400 nm frequency. This is because UVB rays cause direct DNA harm by stimulating the development of cyclobutene pyrimidine dimers and pyrimidine (6-4) photoproducts. The third kind of ray, UVC ray, are more harmful to the skin than UVA or UVB, which is totally consumed by the ozone layer. UV radiation modifies the skin in manners that cause skin immunosuppression that may likewise prompt skin disease [32].

Diagnosis of skin cancer for the most part starts with a visual assessment. The Skin Cancer Foundation and the American Cancer Society suggest month-to-month self-assessments and yearly specialist visits to evaluate for potential skin disease. If a suspicious area in the epidermis is discovered, primary care physicians will examine it first, noting its size, dimensions, structure, outlines, shading, surface, and any drain [33]. Also the physician may likewise analyze close-by lymph hubs to see whether they are augmented. The patients can see a dermatologist who can do more detailed testing and come to a conclusion. The dermatologist may use a special magnification instrument or magnifying lens to examine the shady spot more closely, which is called dermatoscopy. Usually, the skin malignant growth is eliminated in the dermatologist's office. In that time if the dermatologist decides that the skin disease is melanoma or Merkel cell carcinoma, then it is possible that a more vigorous approach is required. The expert ought to have the option to affirm the conclusion

by doing an actual assessment [33-34]. Nonetheless, they will most likely do a biopsy, which is a minor surgery where either part or all of the cancer is taken out so it very well may be checked under a magnifying instrument. This is generally done after a sedative is given. A cell removal permits the dermatologist or plastic specialist to decide the kind of skin malignant growth regardless of whether there's any shot at it spreading to different pieces of the body [34].

Most skin cancer growths are distinguished and revealed before they spread. Skin cancer that has spread to different organs presents the most challenge to treatment. Standard treatments for limited basal cell and squamous cell carcinomas are safe and effective. Small growths can be accurately excised, scratched off with a curette, and then seared, frozen with liquid nitrogen, or killed with low-dose radiation. Applying a treatment containing 5fluorouracil, a chemotherapeutic medicine, or imiquimod, an immune response modifier, to slow the growth for an extended period of time may also function. Larger restricted growths are taken out carefully [35]. In uncommon situations where basal cell or squamous cell carcinoma has started to spread past the skin, growths are eliminated carefully and patients are treated with chemotherapy and radiation. Now and then metastatic (spreading) basal cell skin diseases that can't be treated by a medical procedure or radiation are dealt with orally with sonidegib (Odomzo) or vismodegib (Everidge). Skin malignant growth can be analyzed and treated simultaneously. The growth can be eliminated, and one may not require further therapy in light of the fact that the disease is probably not going to spread [36-37].

Chapter 4

Dietary and Phytochemical Compounds for the Treatment of Skin Cancer

There are many natural resources for medicinal use around the world, many of which have yet to be tapped for possible use in the pharmaceutical business. Plants, animals, microorganisms, and marine life are examples of natural sources. Approximately 25,000

phytonutrients have been identified in studies, including polyphenols, phenolic acids, flavonoids, carotenoids, lignans, coumarins and sterols. Including all these there are many fruits and vegetables, such as nuts, beans, tea, and whole grains are examples of foods which are high in phytochemicals. Despite the fact that most dietary phytochemicals do not operate as pharmaceuticals to treat diseases, studies say that, their use is connected to a number of positive health effects, including a reduced risk of cancer [38-39].

Table 4.1 *Active dietary components and phytochemicals against skin cancer (Adapted from [118])*

Apoptosis promoter	Anti-proliferative	Anti-metastatic
Quercetin	Kaempferol	Amentoflavone
Kaempferol	ECGC	Hinokiflavone
ECGC	Apigenin	Beta-Carotene
Apigenin	Vitamin A	Fucoxanthin
Beta-Carotene	Vitamin C	Vitamin A
Fucoxanthin	Vitamin D	Vitamin C
Vitamin C	Vitamin E	Resveratrol
Resveratrol		Sulforaphane
Curcumin		
Sulforaphane		

In this review, our goal is to provide a quick overview of some of the dietary phytochemicals, emphasizing their key sources, and potential benefits in the treatment and prevention of skin cancer (Table 4.1).

4.1 *Flavonoids*

Flavonoids showed the possibility of suppressing cell proliferation, invasion of cells and chemo-preventive function in melanoma, which is the most devastating type of skin malignant growth. Flavonoids contain polyphenolic structure, which is a part of plant secondary metabolites. They are found in nature through vegetables, fruits, flowers, stems, roots, grains, plant derived beverages like tea and wine etc. On the strength of their antimutagenic, anti-oxidative, anti-inflammatory and anti-carcinogenic characteristics, flavonoids are recently found to be a very essential part of medicine, cosmetic and pharmaceutical industry [40].

Flavonoids' chemopreventive properties are based on their capacity to prevent the formation of new skin malignant growth cells, to stop cancer-causing chemicals from being active, and to reduce compound toxicity by preventing their breakdown. A large number of recent studies have been suggested about the potentials of flavonoids in carcinogenic treatment [41]. Most of the time, flavonoids inhibit malignant growth via activating or inhibiting autophagy transition, especially in apoptosis-resistant affected cells. Flavonoids' protective autophagy nature is becoming a strategy for suppressing malignant growth in the clinical trial for protecting patients from common adverse effects in normal tissues [42]. Natural products, vegetables, and plant-based beverages such as green tea, wine, and cocoa-based items are the best sources of flavonoids in the diet. Flavonoids have been shown to have a wide range of anticancer properties: it modifies reactive oxygen species (ROS) searching protein activities, take an interest in arresting the cell cycle, initiating apoptosis, autophagy, and suppressing malignant cell growth. Flavonoids have a dual function in determining ROS homeostasis: under normal conditions, they activate apoptotic pathways and repress signaling pathways by being suitable with oxidants in affected cells, in addition to functioning as a component for cancer prevention [41-42].

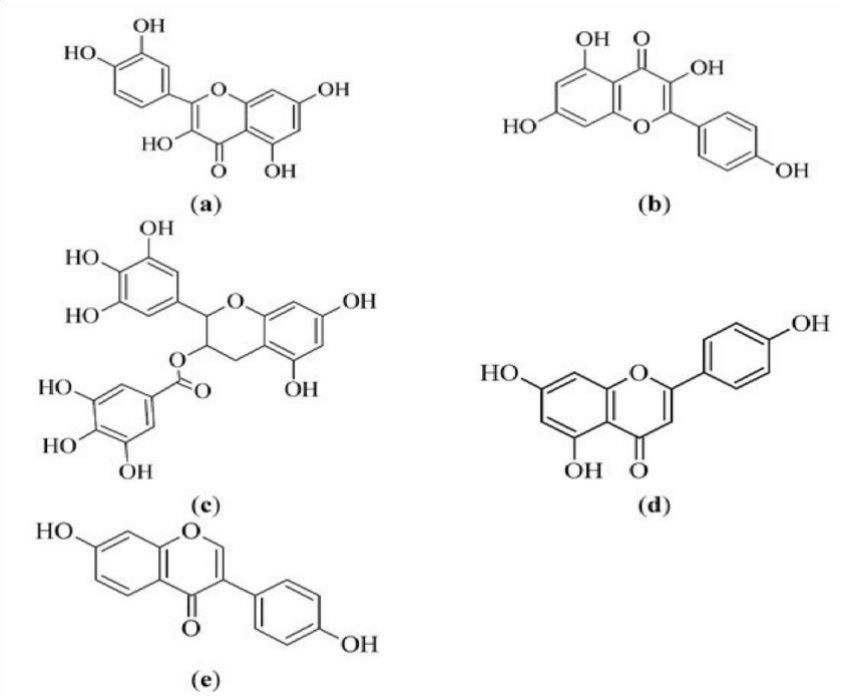


Figure 4.1 *Chemical structure of some of the flavonoids, (a) quercetin, (b) kaempferol, (c) EGCG, (d) apigenin and (e) daidzein (Adapted from [118]).*

4.1.1 *Apigenin*

Apigenin (Figure 4.1d) is a popular flavonoid that has been displayed to slow down UVincited skin malignant growth [43]. It suppresses the basal mTOR activity in the outermost layer of skin, following the stimulation of AMP-activated protein kinase (AMPK). mTOR protein functions as a regulator for the growth of mammals by controlling their metabolic process, so it plays a crucial role in the tumor cells by regulating cell growth, cell proliferation, cell cycle, apoptosis etc [44]. Many studies discovered that apigenin inhibits the UVB-induced mTOR signaling pathway in keratinocytes and mouse skin, which is certainly carried by the AMPK. As an outcome of this it reduces the cell growth or proliferation in outer skin layer by promoting cell apoptosis and autophagy. Interestingly, apigenin doesn't modify UVB-prompted apoptosis. Taken together, research outcomes showed the important role of mTOR inhibition in apigenin-mediated UVB protection, and provided another objective and mechanism for better avoidance of UV-induced skin malignant growth [43-44].

Apigenin has showed its influence as a conclusive chemopreventive agent by reducing the volume and the growth rate of malignant tumors in UVB-induced mouse models along with *in vitro* tests. For instance, it has been seen to repress angiogenesis by suppressing the factors, components and pathways responsible for promoting it. Angiogenesis is a hallmark for cancer, which plays an important role for the metastasis and growth of cancerous cells.

This includes transcription factor HIF-1α, which responds in low oxygen, to elevate oxygen for the survival of tumorigenic cells; development factors like *VEGF, COX2*/prostaglandin E2 pathways, which are key mediators to tumor angiogenesis, helping to facilitate blood vessel growth, increase cell proliferation and migration; and NOS and *IL6/STAT* pathways that stimulate cell growth, gene activation, and survival. *In vitro* results showed that apigenin suppresses angiogenesis through all these different pathways and factors. Specially, the UVB activated reaction of *COX-2* is definitely restrained by apigenin. Moreover, it improves the cell cycle arrest and apoptosis of cancerous cells by activating the action of p53 tumor suppressor gene [45].

Studies indicate that apigenin, which is regulated by the mRNA-restricting protein *HuR*, restores the purpose of anti-angiogenic *TSP1*. *THBS1* is a protein coding gene that activates a glycoprotein which is called *TSP1*. These thrombospondins directly reacts with development factors, molecules and pathways which controls and promotes angiogenic effects. So it has an ability to inhibit the function of *HIF-1α* and *COX*-2 by influencing the regulation of cell proliferation, migration, invasion and activation of apoptosis. In a study on an original SKH-1 hairless mouse model, the function of *THBS-1* has been entirely removed. When it was examined with heavy exposure of UVB ray, the results showed severe skin damage including carcinogenesis. The tests have been also done in mouse with hair layer and pigmented skin, but it couldn't prevent the effect of UVB ray. In both short term and long term carcinogenesis researches it has been seen that the deletion of *TSP1* increase the sensitivity of skin to UVB ray. Additionally, in the SKH-1 model, the application of apigenin has inhibited the carcinogenesis in the wild type caused by UVB.

But for the TKO mice apigenin haven't work in the same way. Now the TKO (TSP1 KO) mice is presented with severe skin inflammation, because of the increased neutrophils, macrophages and elevated inflammatory cytokines IL-6 and IL-12. Finally, further results

showed that, when standard amount of *TSP1* expression was found in the skin of wild type mice which was exposed in UVB ray, topical application of apigenin can lessen the function of inflammatory cytokines. These revelations can lead to the deduction that *TSP1* is a key component of apigenin's anticancer or chemopreventive properties in skin, distinctively for its anti-inflammatory action *in-vivo* [45-46].

4.1.2 *Kaempferol*

Kaempferol (Figure 4.1b), a member of flavono group, is also known as tetrahydroxyflavone, as it has four hydroxyl groups in it. Kaempferol has both antioxidant and anti-inflammatory characteristic, which can function as antibacterial agent, human metabolite of urinary, xenobiotic, blood serum etc. and plant metabolites. It is found in different kind of fruits, vegetables, beverages like, apple, grape, broccoli, tea etc. Recently, it is in under observation for cancer treatment, though its role as a chemopreventor in malignant growth is still unspecified [47].

According to researches of ATP analysis and kinase test information from *in vitro*, it is found that kaempferol represses the *RSK2* and *MSK1*. *RSK2* and *MSK1* both are serine/threonine kinase which mediate gene activation, cell proliferation, cell differentiation, regulate gene expression and activation by regulating the transcription factor CREB and gene activation through histone H3 phosphorylation. So the kaempferol agents bind in the ATP regulating portion, where the *RSK2* and *MSK1* kinase are present and restricts their kinase activity. Further researches, *in vitro* tests from mouse skin cells demonstrated that, kaempferol acts as a strong inhibitor of UV induced skin carcinogenesis. It is acknowledged that focusing on *RSK2* and *MSK1* restraining, kaempferol plays an important role as a novel chemo preventive specialist for UV-activated skin malignancy. Through the reduction of UV activated phosphorylation of Cyclic adenosine monophosphate (cAMP) reactive restricted protein *CREB1* and H3, it restrains *RSK2* and *MSK1* kinase activities [48]. Kaempferol is a flavonoid with anti-oxidant characteristics that has been touted as a chemopreventive specialist, while there is little data of its effectiveness on UVB-induced photocarcinogenesis [47].

Researchers also analyzed that kaempferol can suppress Src kinase activity by restricting the *COX-2* expression which is activated through UVB ray. Src is a protein tyrosine kinase that has been seen to increase the growth, and metastatic potential of cancerous cells. Additionally, *MAPK, JNK,* and *ERK* regulate key cellular activities in cancer; these kinase enzymes and pathways control gene expression, cancerous cell growth, promote cancerous cell survival, and protect cancerous cells from radiation which results in the inhibition of apoptosis and induction of DNA damage repair respectively. The test result in mouse skin epidermal JB6 P+ cells revealed that, kaempferol reduced the UVB-incited *COX-2* protien expression and actitivities of *Cox-2* and activator protein 1(AP-1), including the inhibition of UVB- activated phosphorylation of *ERKs, JNKs, MAPKs* etc. It also found that some other UVB-incited phosphorylation of MAPKs can be inhbited by kaempferol, though the controller of *MAPK*, Src kinase was uninfluenced. Later, more studies have done in both *in vitro and ex vivo* and the *in vivo* test has suggested that the inhibition that kaempferol is done in UVB-induced *COX-2* expression, it occurs through slowing down Src kinase activity. Also further test on this revealed that, kaempferol effectively removes the ATPrestricting site of Src. Altogether, these outcomes suggested kaempferol is an effective chemo preventive specialist against skin malignant growth through its inhibitory communication with Src [49].

4.1.3 *Quercetin*

Quercetin (Figure 4.1a) is a type of flavonoid that comes from nature and broadly exists in daily diet [54]. Past examinations have found that quercetin has many impacts like inhibiting disease and preventing oxidation. Both *in vivo and in vitro* tests have shown that quercetin can apply against cell growth by modifying cell cycle movement, repressing cell proliferation, advancing apoptosis, inhibiting angiogenesis and metastasis movement, and influencing autophagy [50-51]. Quercetin is a type of phytochemical that is broadly found in food varieties which is consumed every day. It has antioxidant activity inside human body. A broad range of people consume it as a dietary supplement for boosting immunity, maintaining good health, fighting inflammation and allergies. It is commonly found in plants, spices, beverages like, apple, vegetable, berries, cherries, coffee green tea, red wine, broccoli etc. [52].

Quercetin has shown effective results in blood sugar control, chronic brain disorder and cancer treatment. It also has a long list of pharmacological applications, including cancer prevention, anti-diabetic, anti-inflammatory, and anti-proliferative properties. High level of Free radicals in human body can cause cellular damage. For instance, it can give rise to chronic disorders like heart disease and cancer. In quercetin, it has a catechol and a -OH at C3 position, which provides its antioxidant characteristics, and these antioxidants can look for free radicals and neutralize those. Various bioactive molecules like lipids, alcohols and carbohydrates are responsible for producing quercetin. And, multiple researches suggested a few pathways for quercetin to work on treating malignant development of skin [51-52]. A recent study discovered that tyrosinase enzyme are expressed in melanoma cells and can metabolize polyphenolic compounds, and this opens a door for polyphenol based therapy in melanoma. Now, other than being a polyphenolic compound, quercetin has showed proapoptotic and antiproliferative activity for cancers cells in other researches. Since, tyrosinase can metabolize polyphenolic compound like quercetin, and its relation with pigment changes is used to target quercetin for treating melanoma by promoting anticancer activity [53]. Previous research has linked the consumption of quercetin-rich foods to a lower risk of cancer disease. Similarly, using natural products that contain quercetin, such as apples and citrus natural product juices, slows the progression of skin cancer. Several studies have looked at the cytotoxic effects of quercetin on damaged skin cells *in vitro* and *in vivo*. While quercetin is not harmful to healthy cells, it has been discovered that it is cytotoxic to cancerous cells, and that various compounds of quercetin have been proved as a good specialist for skin cancer treatment. Consequently, it can be concluded that chemopreventive and therapeutic characteristics of quercetin work against skin malignant growth and to sum up, probably through these latest discoveries this normal compound represses this skin cancer disease [52-53].

4.1.4 *Epigallocatechin*

Epigallocatechin-3-gallate (ECGC) (Figure 4.1c) has shown anti-cancer effects in some models of skin cancer, and trials are being conducted to see whether it has cytotoxic effects on affected cells. Researchers' recent insight on this topic is that the chance of anti-skin

cancer-causing effects of EGCG are mediated through its implications for β-catenin labeling since β-catenin is elevated in skin growths [54-55].

β-catenin activates the growth of tumors by suppressing *p53* expression and T-cell response. Studies suggested that focusing on the inactivation of β-catenin labeling by the treatment of ECGC on A431 and SCC13 human skin malignant cells can promote cell death and reduce cell suitability [55]. On the other hand, serine and other serine/threonine protein kinases like Glycogen synthase kinase 3 β (GSK3 β) and Matrix metalloproteinases (MMP) help to provide precursors for cancer cell growth, potentiate cell proliferation, survival, influence tumor growth and metastasis by destroying matrix barrier and increasing angiogenesis respectively [61]. It has been observed that β-catenin inactivation by EGCG reduces the basic serine deposit and phosphorylation of *GSK3 β* through upgrading the levels of casein kinase 1α also lessens the quantity of *MMP1, MMP2*. The application of ECGC on A431 and SCC13 skin cancer cells, promotes the siRNA of βcatenin to be removed which reduced the cancer cell expansion and stability [56-57].

Further researches revealed that the TNF Receptor-Associated Factor 6 (*TRAF6*) is an overexpressed enzyme in melanoma cancer which increases the growth and metastasis of cancer cells. In a study, it is demonstrated that ECGC can bind to multiple amino acid residues of TRAF6, though there is chance of destroying the bond between *TRAF6* and ECCG by the mutation of some of this residues like Asp57, Gln54. Still, further tests of *in vitro* and *in vivo* has suggested that ECGC can reduces the ligase activity of TRAF6, resulting in suppressing the cell growth and metastasis of malignant cells. *NF-κB* is directly and indirectly involved with cancer development. It controls the expression of multiple genes that can cause cancer cell growth, angiogenesis, and metastasis including epigenetic alterations, also the phosphorylation of iκbα and *p-TAK1* tumor suppressor gene can cause cell proliferation of cancer cells and rise their metastatic behavior. Moreover, this binding of ECGC can promote the inactivation of *NF-κB* and suppress the phosphorylation of *IκBα, p-TAK1* expression, which leads to the prevention melanoma [58].

4.1.5 *Daidzein*

Daidzein (Figure 4.1e) is a member of 7,3′,4′-trihydroxyisoflavone (THIF) group which is found in soybean. It also found in organisms like *Pericopsis elata, Thermopis lance* etc. It is a plant metabolite and antineoplastic agent that have both phytoestrogenic and antioxidant characteristics [59]. Very limited amount of information is found about daidzein and its metabolites' chemopreventive properties in UVB-induced skin cancer growth. The effectivity of 7,3′,4′-trihydroxyisoflavone (THIF) on its cancer preventive nature is tested on mouse skin epidermal JB6 P+ cells. Though few researches have been done on daidzein and it metabolites [64-65]. Still the results from western blot and kinase analyses of JB6 P+ mouse skin cells showed that 7,3′,4′-THIF effectively inhibits cyclooxygenase 2 (*COX-2*) expression by regulating *NF-κB* activity, and it can block the activity of phosphorylated mitogen activated protein kinase kinase 4 (*MKK4*). Phosphorylation of *MKK4* can increase the metastasis of cancer cells and COX-2, and NFκB can increase cancer proliferation, and angiogenesis; hence it seems that 7,3′,4′-THIF can prevent cancer. It was discovered that routine activities of 7,3′,4′-THIF can promote cancer preventive features. It slowed the rate, variety, and volume of UVB-activated mouse skin malignant developments in a mouse skin carcinogenesis model. Another metabolite of daidzein is 6,7,4'- trihydroxyisoflavone [61-62].

In a study on MCF10CA1a human estrogen receptor (ER) negative skin affected cell, is found that, 6,7,4'-trihydroxyisoflavone can arrest cell cycle. Cyclin-subordinate kinases (CDKs) like *CDK1, CDK2*, cyclins A, B, E which is managed by the 6,7,4'- trihydroxy isoflavone are connected with the S-and G2/M stages of cell cycle. 6,7,4'- trihydroxy isoflavone can promote degradation of ADP-ribose polymerase which leads to the rise of apoptotic protein and upgrades receptor4 pathway. These events can cause the death of cell by capturing cell cycle at S-and G2/M stage. Altogether, These findings suggest that daidzein's metabolite, 6,7,4'- trihydroxy isoflavone, can be an effective compound in preventing ER-negative skin melignancies, repressing cell multiplication by capturing cell cycle at S-and G2/M stages, and initiating death in affected MCF10CA1a human skin cells [60, 63].

4.2 *Carotenoids*

The epidermis is an active site for cholesterol storage, which is required for the epidermal barrier to operate properly. Carotenoids generally accumulate in the epidermis after being absorbed in the stomach and transported to the skin. The cholesterol transporters SR-B1 of the basal layers are assumed to transfer carotenoids into the epidermis [64].

Carotenoids are fat-soluble compounds found in nature mostly from green herbs, but these are also biosynthesized in some microbes. Carotenoids are non-polar hydrocarbons. More than 800 carotenoids has been discovered, and 20 among those carotenoids like α-carotene, β-carotene, lutein, lycopene, zeaxanthin, and β-cryptoxanthin are used in researches for the health of human. Both α-β-carotenes, and β-cryptoxanthin are vitamin A carotenoids with various levels of provitamin action [65]. Molecule like *NF-κB* /p65 mitogen-initiated protein kinase (MAPK), the Janus kinase (JAK), signal transduction activator of transcription (STAT), and the nuclear factor erythroid 2-related element 2 (Nrf2) play a crucial role in cancer progression from starting the regulation of gene expression, tumor cell activation, growth to promoting the cells invasion, metastasis and resistance to apoptosis. UVR affects the skin cells by targeting these molecules, which harms the integrity of cells [66].

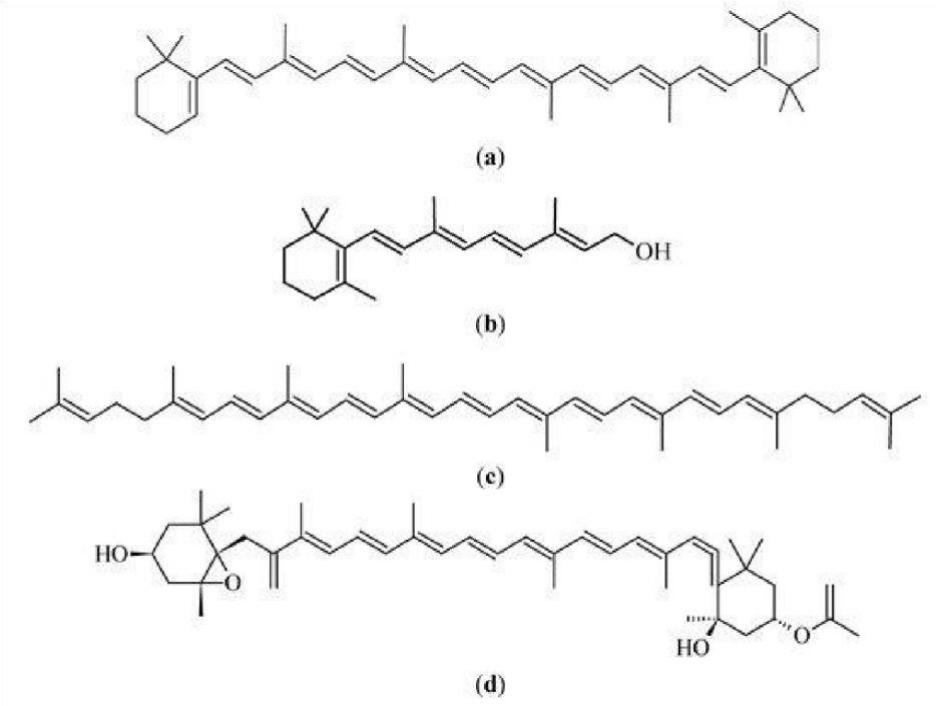


Figure 2.2 *Chemical structures of some of the carotenoids: (a) β-carotene, (b) retinol, (c) lycopene and (d) fucoxanthin.(Adapted from [122])*

Studies have been done on the photo protective effect of carotenoids through dietary supplement or topical application. The majority of the carotenoids reflect the longer wavelengths like yellow, red and orange through absorbing the blue-green, violet (the spectrum between 400-500 nm) [65, 67]. β-carotene, xanthophyll, and lycopene are this kind of pigmented carotenoids. There are also carotenoids which are not pigmented e. g. phytoene and phytofluene; topical application of these carotenoids can provide cover for UVB and UVA range. Apart from that, carotenoids can inhibit the harmful effects of ROS by promoting photo inactivation of hemoglobin oxidation, lipid peroxidation, and DNA damage. Moreover, these components meddle with UV light-activated pathways and suppress cell and tissue growths. The possibility of endogenous photoprotection suggests that the active compound is accessible in small amounts at the target region. To conclude, elements of carotenoids are significant because they control pharmacokinetic parameters like assimilation, dissemination, digestion and influence the level of the active compound in the skin [68-69].

4.2.1 *Lycopene*

Lycopene (Figure 4.2c), the compound responsible for the primary color in tomatoes, has the strongest cell-reinforcing properties of all the carotenoids. It has a distinctive structure and chemical characteristics [70]. Lycopene is commonly present in all type of regular dietary sources, and the majority of lycopene is available in cis-structures of human blood and tissues due to compound reactions of the double bonds [71]. When compared to other carotenoids, lycopene has been found to be a more stable and reactive oxygen species. The amount of lycopene in blood and food has been linked to the prevalence of a few diseases, and the cancer-prevention agent feature of lycopene is thought to be primarily responsible for its obvious value [72].

Recent examinations have demonstrated that the anticancer component of lycopene is also recognized as a significant factor for inhibiting growth progression, including the restriction of cellular growth, inhibition of cell cycle mobility, progression of apoptosis, inhibition of cell invasion, angiogenesis, and metastasis during the phase of detoxification.

The effect of lycopene are identified using the direction of a few signal transduction pathways, such as the *PI3K/Akt* pathway, and observing the balance of insulin-like growth factors framework, the secretion of sex steroid chemicals, the change of significant chemical bonds, and the modification of mitochondrial tasks. These important discoveries have proposed that lycopene might be linked to a reduced risk of various kinds of malignant growth [73-74].

The effects of Lycopene enhanced tomato extract (LycT) on chemically induced skin cancer in mice were investigated in a recent study. 7,12-Dimethylbenzaanthracene (DMBA) and 12-O-tetradecanoyl phorbol-13-acetic acid derivation (TPA) are molecules that promotes the tumor formation by suppressing immune system. In this study, both DMBA and TPA were applied topically on mouse skin to induce skin tumor, along with that LycT was administered orally to the mice. The mice were divided into two groups, where the controls were DMBA/TPA, *LycT* and *LycT*+ DMBA/TPA. This was continued for in total eight weeks, where DMBA was given twice a week for two weeks, TPA was given twice a week for eight weeks, and LycT was given every day. After eight weeks, the results were compared between the groups depending on their controls. Results showed that LycT reduced the protein and mRNA expression of genes that helps in angiogenesis, including the reduction of angiopoietin-2, *VEGF, BFGF* (basic fibroblast growth factor) in *LycT*+ DMBA/TPA group. Also the result of histochemical study showed that during skin carcinogenesis and chemoprevention by LycT, extracellular matrix components fibrous proteins and mucopolysaccharides were regulated in this group. The increased protein expression of connexin improved the cellular communication in the *LycT*+ DMBA/TPA group than the DMBA/TPA group. All these observations were found by decreasing of the epidermal morphometric parameters as well as inhibition of mRNA and protein expression of proliferating cell nuclear antigen. To conclude, the chemopreventive characteristics of LycT was evident by the reduction in cell multiplication borders, binding of angiogenesisrelated qualities, the balance of ECM components, and the expansion of connexin binding [74].

4.2.2 *Fucoxanthin*

Fucoxanthin (Figure 4.2d) is a xanthophyll, which is also a part of the carotenoid group. Fucoxanthin is found in marine organisms as a pigment in the chloroplast of brown algae, seaweeds, diatoms, dinodlagellates etc. It is hypothesized that one reason for coastal inhabitants' longer life spans is their regular consumption of ocean vegetation, particularly earthy colored green growth, which is known to be one of the major sources of fucoxanthin. Fucoxanthin-rich green ocean plants have been studied for their disease-fighting properties [75].

Subsequently, the effect of fucoxanthin on malignant development is intriguing, and some scientists have considered it. The result of studies on fucoxanthin in malignant growth has established that fucoxanthin performs a protective role and inhibits proliferative behavior in various types of disease. Gagez *et al.* have evaluated the natural activities of epoxy carotenoids and fucoxanthin in skin malignant growth cells *in vitro* and represented that fucoxanthin targets on different cells. It was critical to understand the component through which fucoxanthin applied its anticancer-causing function in cells. Several studies have tried to figure out which molecules and pathways fucoxanthin can regulate and found that fucoxanthin has an impact on a range of cell functions, but none has been able to identify a single key mechanism of action [76].

Fucoxanthin has showed a few medical advantages. Considering its strong defense in cancer-causing action, the need to understand the underlying mechanism has become significant. To achieve this goal, a group of scientists conducted research in various cell lines and *in vivo* and discovered that fucoxanthin exerts its anti-proliferative and anticarcinogenic effects via a variety of molecules and pathways, including the *Bcl-2* proteins, *MAPK, NFB,* Caspases, *GADD45*, and a few different factors associated with cell cycle capture, apoptosis, and metastasis. Fucoxanthin has cytotoxic effects on disease cells, which prevents the development of cancerous cell growths and helps in cell apoptosis. Several studies have demonstrated that fucoxanthin targets affected cells only without affecting the healthy cell, which makes its function very specific. As a consequence, Fucoxanthin and its metabolites proved itself as an exceptional chemotherapeutic agent in skin malignancy treatment [76-77].

Some studies have focused fucoxanthin and its metabolites' cell immune boosting properties. Its cell immune boosting property was the first thought to be the fundamental purpose for its prevention of carcinogenesis. Currently, it is accepted that the scope of fucoxanthin's impact is broader and includes a few other natural cycles also [77]. Furthermore, a few studies have shown that fucoxanthin has a positive oxidant effect on malignant development cells, resulting in the production of free radicals, which suggests that this is one of the methods by which it protects against disease cells. Kotake-Nara *et al.* have assumed that the pro-oxidant actions of fucoxanthin and other carotenoids used in their investigation may justify the acceptance of apoptosis in malignant growth cells. Nonetheless, in their review they discovered that fucoxanthin causes comparable apoptosis in promyelocytic leukemia cell lines. However based on their findings in *HL-60* cell lines, they concluded that reactive oxygen species (ROS) isn't the normal pathway for apoptosis. On the other hand, Kim *et al.* have also noticed Fucoxanthin has been found to inhibit the development of leukemia cell lines, and scientists linked this to reactive oxygen species (ROS) produced by fucoxanthin, which triggers apoptosis. They observed increased production of H_2O_2 and O_2 as a result of fucoxanthin therapy, as well as an increase in the number of cells with sub-G1 DNA content (demonstrating cell cycle capture in G1 stage). The quantity of apoptotic cells and DNA damage of cells were increased when fucoxanthin was given in combination with a commercial cancer prevention medication N-acetyl cysteine (NAC), indicating that the apoptotic effect of fucoxanthin is due to the production of reactive oxygen species (ROS). Researchers hypothesized that in contrast to the counterpigmentation effect of fucoxanthin, suppression of melanogenesis in melanoma, and tyrosinase movement in UV-exposed guinea pigs, fucoxanthin's fatal activity is mediated by ROS production, which causes death in *HL-60* cells. The protective effects of fucoxanthin on the exposure of human fibroblasts to UVB light were related to fucoxanthin's cell reinforcement movement [76, 78].

4.2.3 *Curcumin*

Curcumin (Figure 4.3) seems to restrain skin disease development and delay the time of growth in the beginning when regulated by either an oral or effective course. This information proposes that curcumin may have chemopreventive potential against skin

disease. Curcumin terminates the development of melanoma skin malignant growth cells. Curcumin restrained malignant growth cell suitability and set off cell progress in three distinctive melanoma cell tests. The higher the portion, the more compelling it is [79-80]. Curcumin seems to restrain skin SCCs development and closes growth movement by suppresssing pS6 activation. The serine/threonine protein kinase *AKT* and the mammalian target of rapamycin (mTOR) both play important roles in cancer cells, increasing cell proliferation and survival while also causing genetic changes in oncogenes and oncogenerelated proteins, which leads to the initiation of cancer cell progression, survival, and metabolism. And both of these biomarkers hyper activation and overexpression can be seen in the cancer cells [80].

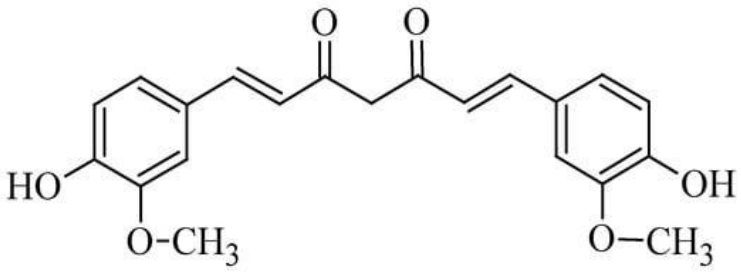


Figure 4.3 *Chemical structure of Curcumin (Adapted from [123])*

Curcumin is a bioactive dietary component that has showed its role for the prevention of cancer in some places [79]. A research was conducted using curcumin to find its chemopreventive properties on squamous cell carcinoma (SCC) of the head and neck (HNSCC). First the test is done on HNSCC and keratinocyte cell line in the absence and presence of nicotine respectively. It is widely known that Nicotine, a genotoxic alkaloid, has showed its function for decreasing the activity of tumor suppressor gene resulting the speed of abnormal growth of new cancerous cells like lung, breast, colon, skin etc. Curcumin's effects have been discovered in the suppression of the *AKT/MTOR* pathway both in presence and absent of nicotine. Along with that, by modifying *pS6* which is a downstream of mTOR activation, curcumin suppressed the growth in *SCC40* cell line. Also, *MMP9* is quite known for its part on promoting tumor progression by destroying matrix barriers of cell line, following to the initiation of metastasis and angiogenesis. In this case, in both in vitro and in vivo, increasing the amount of curcumin to 15 mg for 350 days resulted in suppression of altered cell movements and down regulation of *pS6*, which

was associated to a reduction of *MMP-9*. This was the very first study where curcumin was seen to suppress *AKT/MTOR* pathway including blocking the negative effects of nicotine on malignant cell lines [81-82].

Curcumin, a part of turmeric (*Curcuma longa*), has displayed a variety of antitumor properties. It is a potent inhibitor of ACC migration *in vitro* and *in vivo*. Vascular endothelial growth factor (*VEGF*), framework metalloproteinase (*MMP-2 & -9*), mammalian objective of rapamycin (*mTOR*) and the nuclear factor-κB (*NF-κB*) are key mediators in metastasis and angiogenesis of cancer cells. Another research revealed that curcumin attenuate the affectivity of *VEGF, MMP 2* and *MMP 9*, following the inhibition of angiogenesis in ACC cells. Further study on this case disclosed that this suppression on ACC cells occurs because of the diminution on the *NF-κB* and *mTOR* signaling pathway. Curcumin effectively reduced the *in vivo* development and angiogenesis of ACC xenografts in naked mice, as evidenced by the induction of cell death and a decrease in the thickness of tiny vessels in growing tissues. Furthermore, the activation state of both the *mTOR* and *NF-κB* pathways in ACC tissues was examined, confirming the high initiation of these two pathways in ACC tissues. These findings suggest that future clinical testing of curcumin as a novel chemotherapeutic regimen for ACC is justified [83].

4.2.4 *β-carotene*

β-carotene (Beta-carotene) (Figure 4.2a) is a carotenoid pigment, which is found in many fruits and vegetable in the color orange, red, yellow etc. In most fruits and vegetables, it is found as Vitamin A, which has anti-inflammatory and antioxidant properties. It is also found to prevent diseases like cataracts, skin aging, heart disorders, cancer etc. [84].

Additionally, there has been also seen a connection between vitamin C and β-carotene. A study was conducted on patients with non-melanoma skin cancer who consume alcohol and smoke heavily, with an emphasis on the use of β-carotene and vitamin A. And the results revealed that high intake of food like vegetable, fruit, fish which contain vitamin C, vitamin A and β-carotene can lower the chances of non-melanocytic cancer [84-85].

β-carotene is a type of carotenoid and a significant precursor to vitamin A. Vitamin A is fundamental component for biochemical and physiological cycles in the body including vision, propagation, cell separation and resistance. β-carotene can be obtained as a dietary supplement from green fresh vegetables as well as in a few yellow and orange vegetables and fruits. A significant connection was discovered between the risk of skin disease and a high intake of fish (p=0. 05); vegetables generally (p=0.001); and beans, lentils, and variations (p=0.004). Many studies have showed that consuming fruits and vegetables high in β-carotene has been linked to a lower risk of cancer [86-87]. A research has been done on β-carotene for the prevention of BCC and SCC. 1805 patients with non-melanoma skin cancer have been prescribed to consume 50 mg of β-carotene orally including regular

(yearly) skin checkups. Over a five-year period of therapy and observation showed that, βcarotene does not reduce the development of new skin malignancies on those are at high risk. It was linked with a lower risk of human malignant growth in many investigations using dietary surveys or blood estimations, and it has been shown to have anti-carcinogenic properties in various animal models [88].

β-carotene supplements are not very beneficial to reduce the risk of prostate and nonmelanoma skin diseases. On the other hand, Carotenoids-rich foods are related with a

lower risk of malignant growth in the lungs, mouth, throat, larynx and skin. However, current data are not enough to support the beneficial effect of β-carotene in human cancer. According to researchers, β-carotene is more effective in preventing skin cancer than treating it. It improves the ability of the immune system to fight any disease. Also it has been seen to reduce the harmful effect of UV ray on skin. The Disease Council suggests, individuals should get their dietary necessities from entire food varieties, rather than supplements to boost the immune system [86, 88].

4.3 *Vitamins*

Since the human body is unable to generate vitamins, which are essential compounds for our nutrition, these are consumed through foods and supplements. Vitamins accomplish various functions in human biological mechanisms, which give them their significance. Many cancer researchers have also showed that vitamins have various anti-cancer properties, which is discussed in the following section.

4.3.1 *Vitamin A*

Vitamin A (Figure 4.4) is linked to a variety of health benefits, including bone growth, visual development, and regenerative health, as well as protection from UV rays. Also it assists with skin protection. Vitamin A is a basic nutrient for eye sight. It helps with anticipation of night visual deficiency and decreases the danger for macular degeneration, the main reason for visual deficiency. The fat-soluble nutrient can operate as a powerful cancer preventative agent by shielding the body from free radicals, which are a risk factor for premature aging and chronic sickness. This nutrient is available in various foods, like eggs and chicken, turkey, or liver [89-90].

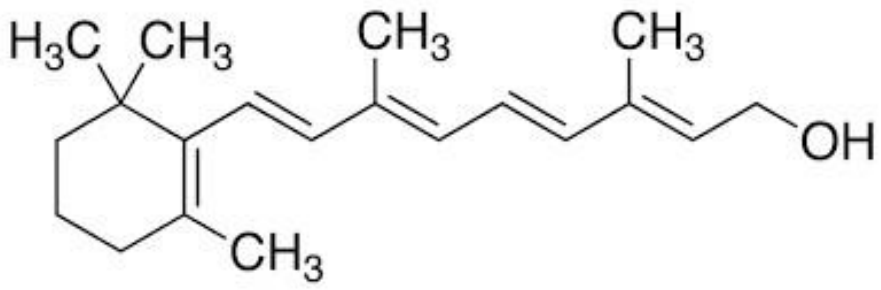


Figure 4.4 *Chemical Structure of vitamin A (Adapted form [124])*

Vitamin A is also called retinol. This nutrient is present in many foods grown from the ground, in the forms of β-carotene, alpha carotene, and β-cryptoxanthin. A few foods grown from the ground that are great component of Vitamin A like yams, carrots, kale, butternut squash, pumpkin, broccoli, apricots, and papaya. Individuals might aid their Vitamin A consumption by using reliable sources such as dietary supplements. Individuals might aid their Vitamin A consumption by using reliable sources such as dietary supplements. However, Adult males should consume no more than 900 micrograms of this vitamin per day, while adult females should consume no more than 700 micrograms per day.

Vitamin A has different form of retinoid (a bioactive molecule) like retinol, retinal, retinoic acid etc. [91]. Also, provitamin A, which can be found in form of β- cryptoxanthin, βcarotene, alpha carotene, can form retinoid inside human body. This form of vitamin A mostly found in the grounds and plants. Vitamin A is composed of two main part called retinoid and carotenoids. Retinoid contain retinol, which is a fat solvent containing yellow pigmentation, which is mostly found form the animal based food source [86, 91]. Retinoid have benefits like increasing the production of collagen in skin, leading to enhancement of the anti-aging effect on skin, slowing aging caused by UV exposure, reducing inflammation, and regulating the growth of the cells. Besides it has been seen to improve many kind of skin conditions like psoriasis, eczema. It plays an important role on the regulation of epithelial cell growth and maintenance. It has also chemo preventive properties in it, especially on those which are artificially made [92].

Researches presented multiple epidemiological data that demonstrate that vitamin A or retinoid can be used to treat and prevent cutaneous squamous cell cancer. In both precancerous and dangerous sores, retinoid inhibit the growth of cells and activate a huge

number of downstream labeling pathways that go straight to apoptosis, development capture, and cell separation. Retinoid are considered as chemo preventive specialists against malignant growth parts in body, including head and neck, skin, and liver. Researchers' investigations of UV light–initiated skin malignant growth have given reliable proof of the anticancer impact of carotenoids [93-95].

4.3.2 *Vitamin C*

Vitamin C (Figure 4.5) is a water-soluble chemical that is commonly used as a dietary supplement and has been found to have anti-disease qualities. Humans and most other animals cannot produce vitamin C inside their body, so it has become a very popular and common dietary supplement for human being around the world. It is also known in the name of L-ascorbic acid. Since human cannot synthesize vitamin C by themselves, they fulfill their need of vitamin C via food and dietary supplement. It is found in vegetable, fruits, beverages like broccoli, orange, kiwi, grape, tomato, green pepper, juices of the fruits that have it. In human skin vitamin C is very important for the skin regeneration [94]. It can synthesize collagen and other type of protein. Additionally, it can perform as free radicals, which tends to promote it antioxidant activity. Researches has shown that it is very essential for our immune function, including its role on preventing different kind of oxidative stress related disease, heart disease, cancer etc. Further studies on vitamin C for the prevention and treatment of UV induced non-melanoma skin cancer showed that it promotes the effectiveness of anti-cancer drugs, increases resistance to triggers of DNA damage and lipid peroxidation, and protects photo damage on mammals like mice cells [94-95].

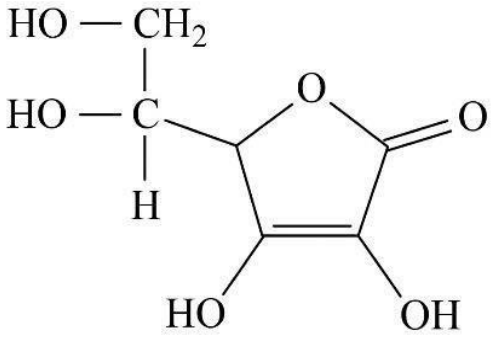


Figure 4.5 *Chemical structure of vitamin C (Adapted from [125])*

Vitamin C has been used in selective medicine for skin malignant growths, despite its lack of efficacy in clinical trials and the unexplained effects on cells structural disease. Vitamin C was found to initiate cytotoxicity against tumors. The component's activity has not been completely clarified, and the effects of Vitamin C on human harmful melanoma have not been analyzed [96]. Vitamin C showed cytotoxicity against the Vemurafenib-resistant cell line *A2058* and *SK-MEL-28.* It was observed that Vitamin C focuses on advanced cell development, metastasis, and cell cycle progression. Interestingly, Vemurafenib activated the *RAS-RAF-MEK-ERK* labeling pathway in the Vemurafenib-resistant *A2058*. Vitamin C canceled this activation when provided as treatment.

High-concentration intravenous Vitamin C (IVC) therapy is broadly utilized in malignant growth patients by associated and voluntary pharmaceutical experts. The most continuous sign for IVC treatment is a result from the dependence in its efficacy as a strong defense against malignant growth, which also improves chemo sensitivity of affected cells and lowers chemotherapy-related toxin levels. Vitamin C showed synergistic cytotoxicity with Vemurafenib against the Vemurafenib-resistant *A2058* In an *in vivo* study, a lower dose of vitamin C (equal to 0. 5 g/70 kg) given orally accelerated melanoma growth. So, the researchers assumed that depending on the concentration, vitamin C may have a pro- or anti-melanoma effect. The mix of vitamin C at high amount and Vemurafenib is promising in defeating the melanoma development [96-97].

In a current review the impacts of vitamin C in human melanoma *A375* cells and the component's basic impacts were examined. Vitamin C strongly suppresses human melanoma A375 cell multiplication by activating apoptosis in *A375* cells. Acceptance of apoptosis was identified with caspase9 and caspase3 initiation and the mitochondrial layer capability of *A375* cells essentially destroyed through Vitamin C. Moreover, vitamin C initiated apoptosis in A375 cells by enacting the *Bax* and *Bcl2* intervened mitochondrial pathway. These outcomes demonstrate that vitamin C might provide potential assistance to cancer drugs for treating patients with melanoma [98]. There are various studies that demonstrated the impacts of vitamin C as a protective treatment for different disease, indicating the utilization of the compound alone as an expected therapy to cure malignant

growth. Mark Levine *et al.* at The National Cancer Institute showed that vitamin C killed affceted cells while causing less harm to good cells [96, 98].

Moreover, vitamin C has been displayed to starts cell apoptosis in different kinds of malignant growth cells, including mesothelioma, pancreatic disease, leukemia and renal cell carcinoma cells. Taken together, the discoveries of this large number of studies demonstrate that high vitamin C portions might prevent the development of cancer cells. High vitamin C dosages increased the amount of reactive oxygen species (ROS) in affected cells bringing about the apoptosis of these cells. Nonetheless, the nuclear structure through which Vitamin C influences melanoma cells are not totally perceived [98].

4.3.3 *Vitamin D*

With numerous advantageous health effects, vitamin D (Figure 4.6) is a fat-soluble vitamin that dissolves in fats and oils. Vitamin D, also known as the "sunshine vitamin," which is a special prohormone found in humans that is formed on the skin when exposed to ultraviolet light from the sun. Bone growth, immune system, and cell proliferation have been linked with the function of vitamin D [105-106]. It is mainly derived from 7dehydrocholesterol, due to sun exposure which is converted into pre-vitamin D_3. Healthy foods that are rich in vitamin D3 include salmon, mackerel, bluefish, cod liver oil, mushrooms, egg yolks, and yeasts. Also ergocalciferol, cholecalciferol, calcidiol, and calcitriol are the different forms of vitamin D [118].

People who have less amount of Vitamin D in their blood have high risk of two skin disease types in particular i.e. basal cell carcinoma and melanoma. The risk of squamous cell carcinoma, a kind of skin malignant growth that is most directly connected to sun exposure, was lower in people with high blood levels of Vitamin D. Vitamin D controls anticancer effects. Protecting somebody's skin from sunlight to avoid skin cancer may result in lower Vitamin D levels [99-100]. Vitamin D metabolites can promote undefined and diverse mechanisms to prevent disease e.g. repairing activities for DNA damage, cell apoptosis of toxic cells, suppression proliferation and angiogenesis of cells. Recent discoveries proposed that the anticancer effects of Vitamin D inside squamous cell carcinoma includes the *DDIT4-mTOR* catabolic labeling pathway to improve cell autophagy. Since mTOR

translocation and cell breakdown are controlled as part of the DNA damage reaction, this shows that Vitamin D can restrain mTOR to prevent malignant development which is clinically important [101-102].

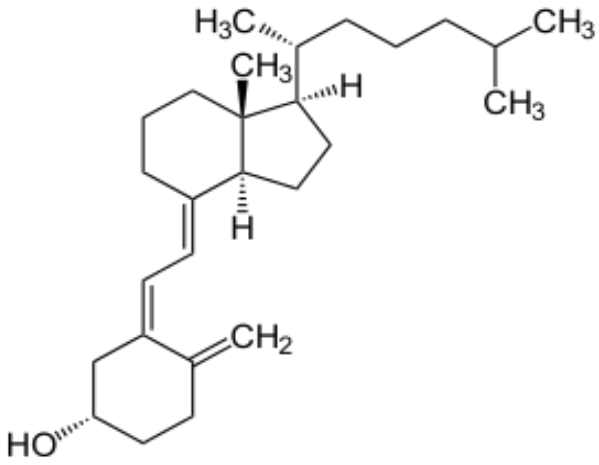


Figure 4.6 *Chemical structure of vitamin D (Adapted from 126)*

Generally, the studies till now recommends that presence of Vitamin D through daylight exposure and supplementation are helpful for human health despite malignant growth. Daylight exposure of the skin is related to two dangers and advantages. On one hand, daylight bright (UV) radiation can cause skin disease through signature DNA transformations [103]. Then again it is possible that 7-dehydrocholesterol is involved in the skin to promote an endogenous synthesis of Vitamin D to have anticancer effects. To avoid skin cancer, shielding one's skin from sunlight may result in low Vitamin D levels competing with regular sun exposure practices. During exposure to daylight, the bright B photons enter the skin and photolyze 7-dehydrocholesterol to pre-vitamin D3 which thusly is isomerized by the internal heat levels to Vitamin D3. The majority of individuals have relied on the sun to fulfill their Vitamin D requirements. Previtamin D3 synthesis is influenced by skin color, sunscreen use, aging, the time of day, season, and area [104-105]. Vitamin D deficiency was formerly assumed to be cured; nevertheless, it is now estimated that over half of the world's population is suffering from Vitamin D deficiency. Vitamin D deficiency causes developmental problems and rickets in children, as well as hastening and intensifying osteopenia, osteoporosis, and increasing the risk of a fracture in adults. Other serious consequences of the Vitamin D deficiency include- increased risk of normal cancers, immune system diseases, irresistible infections, and cardiovascular disease [106]. Exposure to daylight plays a significant part in giving sufficient Vitamin D provides nutrients to the majority of the number of inhabitants on the planet, incorporating the people who live in places that keep dairy, margarine, and oat items with vitamin D [100]. It is

proven that previtamin D3 goes through a thermally prompted isomerization of vitamin D3 that requires 2-3 days to occur. During the exposure to daylight, provitamin D3 is proficiently changed over to vitamin D3. Provitamin D3 is photolabile, exposure to daylight causes it to isomerize, converting it to lumisterol. Subsequently around 10-20% of the provitamin D3 focuses eventually end up as vitamin D3. The cutaneous formation of this nutritional chemical is largely influenced by maturation, sunscreens, frequent changes, season of the day, and location [105].

4.4 *Sulforaphane*

Sulforaphane (Figure 4.7) is a molecule rich with sulfur from the isothiocyanate group. Unlike some other bioactive compound, sulforaphane can be produced in human body, and it is also found in green vegetables like cabbage, bok choy, and broccoli. It has antiinflammatory properties, and because of this nature it is been useful for prevention and treatment of many types of cancer including skin cancer [107]. A study has been done to see the efficiency of sulforaphane consumption for the treatment of skin malignancy on the bare dorsal skin of mice. 9 mol of sulforaphane were given to each mouse per day orally, including the application of 7,12-dimethylbenzaanthracene and croton oil in mouse dorsal skin. The sulfatase-2 and glypican-3 molecule was seen to play crucial role in the proliferation, invasion, and angiogenesis of cancerous cells, however Heparan sulfate proteoglycans (HSPGs) demonstrated many positive roles in cancer progression. In this study the consumption of sulforaphane daily resulted in inhibition of sulfatase-2, glypican3 and elevating the HSPGs amount in cell. Along with this, sulforaphane has also seen to destroy the effectiveness and protein articulation of *NFκB, TNF-α, IL-1β* and caspase-3, which play major roles in the metastasis and invasion nature of cancer cells. Altogether this study proved that sulforaphane can reduce the regulation of provocative and apoptotic pathways of UVR induced skin cancer [108].

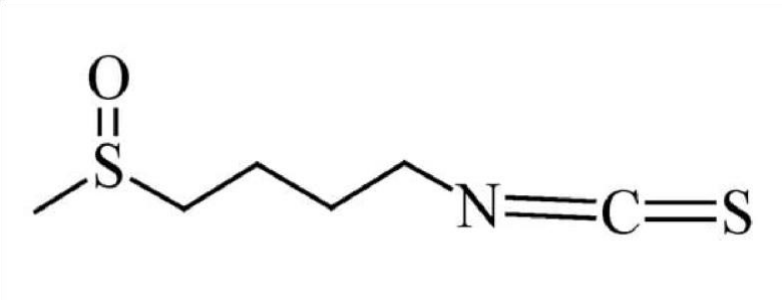


Figure 4.7 *Chemical structure of sulforaphane (Adapted from [127])*

It is suggested that by allowing cancer-preventive proteins to receive the storage factor Nuclear Factor E2-related variable 2 (Nrf2), sulforaphane can exert chemopreventive effects. The chemopreventive efficacy of sulforaphane was assessed with the two genotypes in per mouse in *Nrf2 wild-type* ($^{+/+}$) and *Nrf2 knockout* ($^{-/-}$) mice. Before that the researchers found out that 7,12-Dimethylbenzaanthracene/12-O-tetradecanoylphorbol-13acetic acid derivation medicines increase the rate of skin cancers and growth numbers per mouse in the two genotypes. So during the study, 100 nmol of sulforaphane was given once a day for 14 days as a pretreatment which reduced the cancer skin cell progression in $Nrf2^{(+/+)}$ mice. But, sulforaphane pretreatment had no chemoprotective effects in the *Nrf2(-/-)* mice. This finding demonstrated that, sulforaphane can promote the chemopreventive effect on *Nrf2(+/+)* mice, but *Nrf2(-/-)* mice are susceptible to skin carcinogenesis [109].

Sulforaphane [1-isothiocyanato-4-(methylsulfinyl)butane] is considered as a highly effective chemoprevention medication for a variety of malignancies in the skin, prostate, colon, skin, lung, stomach, bladder cancer, cardiovascular disease, neurological diseases, and diabetes. Preclinical studies have focused mostly on sulforaphane, while clinical studies have relied on broccoli sprout arrangements rich in sulforaphane or its biogenic component, glucoraphanin. Pure compounds or food elements have been used to attempt a thorough evaluation of sulforaphane pharmacokinetics and pharmacodynamics [111, 114]. Sulforaphane influences different parts in cells. The activation of the *Nrf2-Keap1* labeling pathway is one important nuclear component activity for sulforaphane, however other activities contribute to the wide variety of adequacy in other animal models [110-111].

4.5 *Resveratrol*

Resveratrol (Figure 4.8) acts as a chemopreventive and antiproliferative agent against a variety of malignant growths, including skin disease, by reducing cell division associated with cancer initiation, progression, and migration, and inducing apoptosis in such cells. Resveratrol, is a polyphenol and phytoalexin formed from plants. It is artificially produced in laboratories as a dietary supplement. Also it is found in fruits like berries, peanuts, grapes; the skin of red grapes is one of the main source of it. Resveratrol has antiinflammatory, antiviral, anti-cancer effects. It has been showed its effectiveness for the treatment of disease like, diabetes, Alzheimer's, cardio vascular disease, cancer etc [112]. Resveratrol has shown its influence in cancer treatment in a broad range. It has the ability to regulate, block, inhibit, and control carcinogenic agents, molecules, and pathways such as cyclooxygenase, hydro peroxidase, protein kinase C, Bcl-2 phosphorylation, *Akt*, central bond kinase, *NF-κB*, framework metalloprotease-9 in cancer cells. Numerous researches has been done in both *in vitro* and *in vivo* for finding out the chemo preventive effects and cytotoxic factors in cancer cells using resveratrol; and it has potency and efficacy on this matter [113-114]. The available preclinical and surgical knowledge about resveratrol, as well as its prospective applicability in lowering the risks associated with a variety of human malignancies, is discussed here.

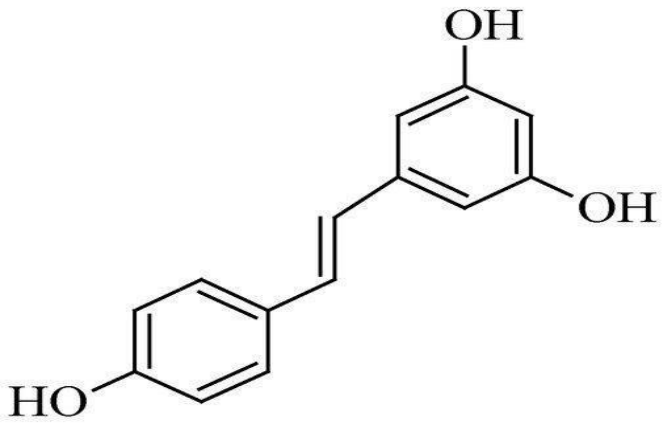


Figure 4.8 *Chemical Structure of Resveratrol (Adapted from [118])*

In a number of cancer bioassays, resveratrol, a naturally occurring phytoalexin released by various plants in response to injury or parasite disease, has exhibited chemo-preventive

effects against malignant growth. For any type of skin malignancy in human, the UV radiation exposure has proved to be the main cause. Previous investigations have showed that resveratrol provides assurance for UVB exposure induced skin cancer in SKH-1 bald mice. In a study the effects of resveratrol for the prevention of skin malignant growth, a test has been done on a SKH-1 bald mice which had a long time UVB exposure. The subjects of the test, SKH-1 mice were exposed to UVB ray for a long time, twice a week; this can be resulted in developing skin malignancy on the mouse skin. For finding the resveratrol's chemo preventive nature, the test is done in two ways. In the first one, 25 or 50 M/0. 2 ml of resveratrol has been topically applied 30 minutes before UVB exposure and in the second one, resveratrol was applied 5 minutes after UVB exposure. And here the resveratrol not only act as a sunscreen but prevent the occurrence cancer hallmarks in the mouse skin [115]. Resveratrol has been shown to have powerful anti-oxidant properties, as well as the ability to inhibit platelet collection and the growth of affected cells. In both synthetically and naturally UVB-induced skin carcinogenesis in mice, its potential chemopreventive and chemotherapeutic exercises have been demonstrated in each of the three phases of carcinogenesis (initiation, progression, and migration). Its ability to regulate multiple targets and labeling pathways has been demonstrated in a number of *in vitro* and *in vivo* studies [113-114].

Chapter 5

Conclusion

The evidence from this review indicates that natural compounds like phytochemicals and dietary may not be as effective as conventional cancer therapy and chemotherapies, but these components' capacity of preventing and intervening in cancer is proven. In this review, only a few of those has been summarized, and there are still a large number of resources that remain in nature that have not been discovered or studied yet. Recently, researchers, doctors and scientists are getting more interested to these natural compounds due to their cost-effective nature, wide availability and potential for modification. Additionally, these phytochemicals derived from natural compounds like medicinal plants and dietary sources have shown some effective anti-cancer activity in both *in vivo* and *in vitro*, which should be clinically proven to bring on favorable clinical effects in humans.

Many studies have also found connections between dietary components and skin cancer. However, since the skin is easily accessible for direct examination and topical therapy, so using phytochemicals to treat skin cancer is important for proving their efficacy. The anticarcinogenic effects of phytochemicals have been showed in recent studies; these compounds have variety of protective actions such as anti-oxidation, anti-inflammation, anti-angiogenesis, anti-metastasis, and cancer stem cell modification.

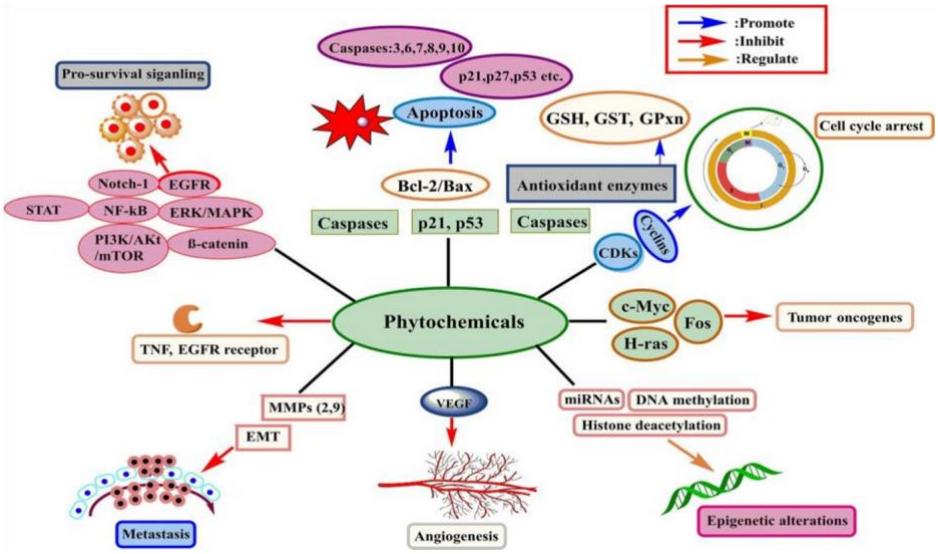


Figure 5.1 *Different phytochemicals are involved in regulating various molecular process to modulate skin cancer (Adapted from [117])*

To act as a barrier against environmental threats, the skin, which is body's first line of defense, must proliferate and differentiate at a rapid rate. Anti-proliferative effects of phytochemicals must selectively target highly proliferating tumor cells to reduce potential adverse skin side effects. These natural compounds inhibit the expression of oncogenes like *Fos genes*, *c-Myc*, *h-ras*, down-regulate *Bcl-2*, and *bcl-x* by increasing the expression of antioxidant enzymes, cyclins, *CDKs*, *Bax* proteins, scavenge ROS, p21, p53 and modulating various signaling pathway like Notch-1, EGFR, *ERK*/*MAPK*, NF-*KB*, *STAT*, ß-catenin, *PI3K/AKT/MTOR*. Furthermore, by inhibiting angiogenesis, metastasis, stopping the cell cycle, suppressing Epithelial-Mesenchymal Transformation (EMT), regulating epigenetic changes, and down-regulating *MMPs*, *COX-2* enzymes, phytochemicals can prevent skin cancer from spreading. They can also induce apoptosis by inhibiting the expression of anti-apoptotic factors like *Bcl-XL* and *X-IAP*, and regulating iNOS and *COX-2*. These phytochemical compounds aid in the protection and reversal of

the detrimental effects of UV radiation from the sun and other environmental carcinogens. As a result, topical application may be an ideal route of delivery, where issues such as improved skin penetration, compounds formulation stability, drug concentration, and treatment length require more research to allow *in vitro* and animal model studies to be translated into beneficial human clinical treatment.

Since certain complementary and alternative medicine therapies are personalized by the individual, evaluating the quality of herbal or supplemental therapies supplied by complementary and alternative medicine is difficult. Additionally, most natural products on the market are not designated as medicines. Since the minimum effective and maximum safe concentrations of CAM are frequently unknown, considerable changes in formulations and bioactivity among batches are predicted due to a lack of control. As a result, it is proposed that healthcare staff use pharmacovigilance to detect potentially dangerous interactions between prescription medications and non-conventional treatments, and that trials is conducted to determine the efficacy of herbal medicines. Recent research has also focused on controlled medication release via topical or oral delivery systems, as well as on the interaction of phytochemicals with conventional skin cancer therapy to help with the complex process of cancer. Combinations of cytotoxic anti-tumor medicines and phytochemical inhibitors may work together to develop tumor growth inhibitory mechanisms.

Based on scientific and epidemiological studies, regular use of these natural chemicals may give good protection against the detrimental effects of solar UV radiation and other environmental skin carcinogens. To detect the molecular effects of newly discovered phytochemicals, preclinical and epidemiological researches are also required. There have been a plethora of research on the efficacy and safety of CAM in skin cancer, but a collection of the available information can accelerate its acceptance. It is anticipated that the presence and access of adequate information and extensive research will help the patients who are interested in CAM to make well-informed decisions and achieve positive results.

Abbreviations

NMSC- Nonmelanoma skin cancer **SCC**-

Squamous cell carcinoma.

UV- Ultra violet.

DNA- Deoxyribonucleic acid.

CAM- Complementary and alternative medicine.

BCC- Basal cell carcinoma.

BRAF- A gene that tells the process of cell growing. Change in this gene can lead to an alteration in a protein that regulates cell growth that could allow the melanoma to grow more aggressively.

MC1R- A gene that provides instructions for making a protein called the melanocortin 1 receptor.

CDKN2A- *A gene* provides instructions for making several proteins.

MCC- Merkel Cell Carcinoma

MCPyV- Merkel cell polyomavirus

UVA, UVB, UVC- Ultra violet ray A, B and C

ROS - Reactive Oxygen species **AMPK**-

AMP-activated protein kinase

mTOR- A member of the phosphatidylinositol 3-kinase-related kinase family of protein kinases.

HIF-1α - (*Hypoxia Inducible Factor 1* Subunit Alpha) is a Protein Coding *gene*.

VEGF - Vascular endothelial growth factor

COX-2 - Cyclooxygenase-2

NOS - Nitric oxide synthases

IL6 - Interleukin 6

STAT - signal transducer and activator of transcription

p53 – a tumor suppressor gene **mRNA** – messenger

ribonucleic acid

THBS-1 – Thrombospondin 1

TSP1 – Trehalose-6-phosphate synthase

SKH-1 – A hairless mouse type

WT- Wild type

BM – Bone Marrow

CD11b+ - an integrin family member which pairs with CD18 to form the CR3 heterodimer.

RSK2 – Ribosomal S6 kinase 2

MSK1- Mitogen and stress activated protein kinase 1

SUV – Solar Ultraviolet **NAC -** N-acetyl

cysteine **cAMP**- Cyclic Adenosine

Monophosphate

H3 – Histone 3

CREB – A cellular transcription factor

AP- 1 – Activator Protein 1

ERKs – Extracellular Signal Regulated Kinases

JNKs- Jun N-terminal kinase

MAPK- Mitogen activated protein kinase

ATP- Adenosine triphosphate

ECGC- Epigallocatechin-3-gallate

DMBA - 7,12-Dimethylbenz(a)anthracene

TPA - 12-O-tetradecanoyl phorbol-13-acetate

BFGF - Basic fibroblast growth factor

LycT – Lycopene enhanced tomato extract

GSK3 β - Glycogen synthase kinase 3 β

MMP- Metalloproteinase

PGE2- Prostaglandin 2 **siRNA**-

Small interfering RNA **GTE**-

Green Tea Extract

MTT- Methyl thiazolyl tetrazolium

MEK- Mitogen activated kinase

GSK- Glycogen Synthase kinase **sClu**

- Secretory Clusterin

THIF- Trihydroxyisoflavone

ER- Estrogen receptor

CDKs- Cyclin-subordinate kinases

ECM- Extracellular Matrix

UVR – Ultra violet ray

RAS-RAF-MEK-ERK - The MAPK/ERK pathway (also known as the Ras-Raf-MEK-ERK pathway) is a chain of proteins in the cell that communicates a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell.

IVC- Intravenously Controlled Vitamin C

HSPGs- Heparan sulfate proteoglycans

TNF- Tumor necrosis factor

Bibliography

1. Sung, H., et al., *Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries.* 2021. **71**(3): p. 209-249.
2. Siegel, R.L., et al., *Cancer statistics, 2022.* 2022. **72**(1): p. 7-33.
3. Foundation, S.C. *Skin Cancer Facts & Statistics*. 2022 [cited 2022 08 March]; Available from: https://www.skincancer.org/skin-cancer-information/skin-cancerfacts/.
4. International, W.C.R.F. *Skin cancer statistics*. 2021 [cited 2022 8 March]; Available from: https://www.wcrf.org/cancer-trends/skin-cancer-statistics/.

5. ASCO, C.N.-. *Skin Cancer (Non-Melanoma): Statistics*. 2022 [cited 2022 8 March]; Available from: https://www.cancer.net/cancer-types/skin-cancer-nonmelanoma/statistics.
6. Leiter, U., T. Eigentler, and C. Garbe, *Epidemiology of skin cancer.* Adv Exp Med Biol, 2014. **810**: p. 120-40.
7. WebMD. *What Causes Skin Cancer?* 2020 [cited 2022 8 March]; Available from: https://www.webmd.com/melanoma-skin-cancer/melanoma-guide/causes-skincancer#1.
8. J.Hall, B., & C.Hall, J. , *Sauer's Manual of Skin Diseases*. 10th ed. 2010, Walnut Street, Philadelphia: Lippincott Williams & Wilkins.
9. Clinic, M. *Skin Cancer*. 2020 8 march 2022]; Available from: https://www.mayoclinic.org/diseases-conditions/skin-cancer/diagnosistreatment/drc-20377608.
10. Foundation, S.C. *Skin Cancer Prevention*. 2022 8 march 2022]; Available from: https://www.skincancer.org/skin-cancer-prevention/.
11. Society, A. *Methods of Treatment*. 1995 8 March 2022]; Available from: http://www1.udel.edu/chem/C465/senior/fall98/Cancer2/methods.html.
12. Society, A.C. *Chemotherapy Side Effects*. 2020; Available from: https://www.cancer.org/treatment/treatments-and-side-effects/treatmenttypes/chemotherapy/chemotherapy-side-effects.html.
13. Choudhari, A.S., et al., *Phytochemicals in Cancer Treatment: From Preclinical Studies to Clinical Practice.* 2020. **10**.
14. Molassiotis, A., et al., *Use of complementary and alternative medicine in cancer patients: a European survey.* Annals of Oncology, 2005. **16**(4): p. 655-663.
15. NHS. *Skin cancer (melanoma)*. 2020; Available from: https://www.nhs.uk/conditions/melanoma-skin-cancer/.
16. Centre, M.C. *What is the Difference Between Melanoma and Nonmelanoma Skin Cancer?* . Available from: https://moffitt.org/cancers/skin-cancernonmelanoma/faqs/what-is-the-difference-between-melanoma-andnonmelanoma-skin-cancer/.
17. ASCO, C.N.-. *Skin Cancer (Non-Melanoma): Introduction*. 2020; Available from: https://www.cancer.net/cancer-types/skin-cancer-non-melanoma/introduction.
18. Foundation, S.C. *Basal Cell Carcinoma*. 2022; Available from: https://www.skincancer.org/skin-cancer-information/basal-cell-carcinoma/.
19. Wong, C.S.M., R.C. Strange, and J.T. Lear, *Basal cell carcinoma.* BMJ (Clinical research ed.), 2003. **327**(7418): p. 794-798.
20. Society, A.C., *What Are Basal and Squamous Cell Skin Cancers?* 2019.

21. Foundation, S.C. *Squamous Cell Carcinoma* 2022; Available from: https://www.skincancer.org/skin-cancer-information/squamous-cell-carcinoma/.
22. Alam, M. and D. Ratner, *Cutaneous Squamous-Cell Carcinoma.* 2001. **344**(13): p. 975-983.
23. Ma, X. and H. Yu, *Global burden of cancer.* The Yale journal of biology and medicine, 2006. **79**(3-4): p. 85-94.
24. Perera, E., et al., *Malignant Melanoma.* Healthcare (Basel, Switzerland), 2013. **2**(1): p. 1-19.
25. MacGill, M. *What to know about melanoma*. 2019; Available from: https://www.medicalnewstoday.com/articles/154322.
26. Britannica, T. *melanoma.*; Available from: https://www.britannica.com/science/melanoma.
27. Foundation, S.C. *Merkel Cell Carcinoma* 2022; Available from: https://www.skincancer.org/skin-cancer-information/merkel-cell-carcinoma/.
28. Clinic, M., *Markel Cell Carcinoma.* 2020.
29. Erovic, I. and B.M. Erovic, *Merkel Cell Carcinoma: The Past, the Present, and the Future.* Journal of Skin Cancer, 2013. **2013**: p. 929364.
30. Ramahi, E., et al., *Merkel cell carcinoma.* American journal of clinical oncology, 2013. **36**(3): p. 299-309.
31. Foundation, S.C. *Skin Cancer Prevention*. 2022; Available from: https://www.skincancer.org/skin-cancer-prevention/.
32. Association, A.A.o.D. *Prevent skin cancer*. Available from: https://www.aad.org/public/diseases/skin-cancer/prevent/how.
33. Clinic, M. *Skin Cancer*. 2020; Available from: https://www.mayoclinic.org/diseases-conditions/skin-cancer/diagnosistreatment/drc-20377608.
34. ASCO, C.N.-. *Skin Cancer (Non-Melanoma): Diagnosis*. 2020; Available from: https://www.cancer.net/cancer-types/skin-cancer-non-melanoma/diagnosis.
35. BPAC. *How to use Flurouracil and imiquimod for non-melanoma skin cancer in a genera; practice setting*. 2017; Available from: https://bpac.org.nz/2017/skincancer.aspx.
36. NHS. *Non-melanoma Skin Cancer- Diagnosis*. 2020; Available from: https://www.nhs.uk/conditions/non-melanoma-skin-cancer/diagnosis.
37. Jockers.Com, D. *Skin Cancer: Symptoms, Causes, and Natural Support Strategies*. 2020; Available from: https://drjockers.com/skin-cancer/.
38. Wang, S., et al., *Can phytochemical antioxidant rich foods act as anti-cancer agents?* Food Research International, 2011. **44**(9): p. 2545-2554.

39. Saeidnia, S. and M. Abdollahi, *Antioxidants: friends or foe in prevention or treatment of cancer: the debate of the century*. Toxicol Appl Pharmacol, 2013. **271**(1): p. 49-63.
40. Center, L.P.I.s.M.I. *Flavonoids* 2005; Available from: https://lpi.oregonstate.edu/mic/dietary-factors/phytochemicals/flavonoids.
41. Panche, A.N., A.D. Diwan, and S.R. Chandra, *Flavonoids: an overview*. Journal of nutritional science, 2016. **5**: p. e47-e47.
42. Raimundo Gonçalves de Oliveira Júnior, C.A.A.F., Mariana Gama e Silva, Érica Martins de Lavor, Larissa Araújo Rolim, Julianeli Tolentino de Lima, Audrey Fleury, Laurent Picot, Jullyana de Souza Siqueira Quintans, Lucindo José Quintans Júnior, Jackson Roberto Guedes da Silva Almeida, *Flavonoids: Promising Natural Products for Treatment of Skin Cancer (Melanoma).* Intechopen, 2017.
43. National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 5280443, A.R.J., 2022 from https://pubchem.ncbi.nlm.nih.gov/compound/Apigenin. *Apigenin*. 2022 [cited 2022 Apigenin]; Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Apigenin.
44. Woo, J.S., et al., *Apigenin induces apoptosis by regulating Akt and MAPK pathways in human melanoma cell A375SM.* Mol Med Rep, 2020. **22**(6): p. 48774889.
45. Zhao, G., et al., *Apigenin inhibits proliferation and invasion, and induces apoptosis and cell cycle arrest in human melanoma cells.* Oncol Rep, 2017. **37**(4): p. 22772285.
46. Mirzoeva, S., et al., *Apigenin Inhibits UVB-Induced Skin Carcinogenesis: The Role of Thrombospondin-1 as an Anti-Inflammatory Factor*. Neoplasia, 2018. **20**(9): p. 930-942.
47. Information, N.C.f.B. *Kaempferol*. 2022 [cited 2022 June 3]; Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Kaempferol.
48. Yao, K., et al., *Kaempferol targets RSK2 and MSK1 to suppress UV radiationinduced skin cancer*. Cancer prevention research (Philadelphia, Pa.), 2014. **7**(9): p. 958-967.
49. Lee, K.M., et al., *Kaempferol inhibits UVB-induced COX-2 expression by suppressing Src kinase activity.* Biochem Pharmacol, 2010. **80**(12): p. 2042-9.
50. Li, Y., et al., *Quercetin, Inflammation and Immunity.* Nutrients, 2016. **8**(3): p. 167167.
51. Ryan Raman. *What Is Quercetin? Benefits, Foods, Dosage, and Side Effects*. 2020; Available from: https://www.healthline.com/nutrition/quercetin#benefits.
52. Salehi, B., et al., *Therapeutic Potential of Quercetin: New Insights and Perspectives for Human Health.* ACS omega, 2020. **5**(20): p. 11849-11872.

53. Harris, Z., et al., *Quercetin as an Emerging Anti-Melanoma Agent: A Four-Focus Area Therapeutic Development Strategy.* 2016. **3**.
54. Singh, N.A., A.K.A. Mandal, and Z.A. Khan, *Potential neuroprotective properties of epigallocatechin-3-gallate (EGCG).* Nutrition Journal, 2016. **15**(1): p. 60.
55. Singh, T. and S.K. Katiyar, *Green tea polyphenol, (-)-epigallocatechin-3-gallate, induces toxicity in human skin cancer cells by targeting β-catenin signaling.* Toxicol Appl Pharmacol, 2013. **273**(2): p. 418-24.
56. Miyai, S., et al., *Biochemical characterization of epigallocatechin-3-gallate as an effective stimulator for the phosphorylation of its binding proteins by glycogen synthase kinase-3β in vitro.* Biol Pharm Bull, 2010. **33**(12): p. 1932-7.
57. Daniel Voskas, L.S.L., James R Woodgett, *Does GSK-3 provide a shortcut for PI3K activation of Wnt signalling?* Faculty Opinions, 2010. **2**(82).
58. Zhang, J., et al., *Epigallocatechin-3-gallate(EGCG) suppresses melanoma cell growth and metastasis by targeting TRAF6 activity*. Oncotarget, 2016. **7**(48): p. 79557-79571.
59. Information, N.C.f.B., *Daidzein.* 2022.
60. Iovine, B., et al., *Synergic Effect of Genistein and Daidzein on UVB-Induced DNA Damage: An Effective Photoprotective Combination*. Journal of Biomedicine and Biotechnology, 2011. **2011**: p. 692846.
61. Lee, D.E., et al., *7,3',4'-Trihydroxyisoflavone, a metabolite of the soy isoflavone daidzein, suppresses ultraviolet B-induced skin cancer by targeting Cot and MKK4.* J Biol Chem, 2011. **286**(16): p. 14246-56.
62. Lee, D.E., et al., *7,3',4'-Trihydroxyisoflavone inhibits epidermal growth factorinduced proliferation and transformation of JB6 P+ mouse epidermal cells by suppressing cyclin-dependent kinases and phosphatidylinositol 3-kinase.* The Journal of biological chemistry, 2010. **285**(28): p. 21458-21466.
63. Lee, J.H. and H.J. Lee, *A daidzein metabolite, 6,7,4'-trihydroxyisoflavone inhibits cellular proliferation through cell cycle arrest and apoptosis induction in MCF10CA1a human breast cancer cells.* Journal of the Korean Society for Applied Biological Chemistry, 2013. **56**(6): p. 695-700.
64. Balić, A. and M. Mokos, *Do We Utilize Our Knowledge of the Skin Protective Effects of Carotenoids Enough?* Antioxidants (Basel, Switzerland), 2019. **8**(8): p. 259.
65. Jane Higdon, P.D. *α-Carotene, β-Carotene, β-Cryptoxanthin, Lycopene, Lutein, and Zeaxanthin*. 2005; Available from: https://lpi.oregonstate.edu/mic/dietaryfactors/phytochemicals/carotenoids.
66. Qu, X., Y. Tang, and S. Hua, *Immunological Approaches Towards Cancer and Inflammation: A Cross Talk.* Frontiers in immunology, 2018. **9**: p. 563-563.
67. Academy, K. *Light and photosynthetic pigments*. 2015; Available from:

https://www.khanacademy.org/science/biology/photosynthesis-in-plants/the-lightdependent-reactions-of-photosynthesis/a/light-and-photosynthetic-pigments.

68. Greenberg, E.R., et al., *A Clinical Trial of Beta Carotene to Prevent Basal-Cell and Squamous-Cell Cancers of the Skin.* 1990. **323**(12): p. 789-795.
69. line, H., *Carotenoids: Everything You Need to Know*. 2017.
70. Nissar, S. *Lycopene*. 2022; Available from: https://www.sciencedirect.com/topics/agricultural-and-biologicalsciences/lycopene.
71. Brandon Petrovich, R. *What Is Lycopene? A Compound That Could Prevent Certain Diseases*. 2022; Available from: https://www.verywellhealth.com/lycopene-health-benefits-4684446.
72. Qi, W.J., et al., *Investigating into anti-cancer potential of lycopene: Molecular targets.* Biomedicine & Pharmacotherapy, 2021. **138**: p. 111546.
73. van Breemen, R.B. and N. Pajkovic, *Multitargeted therapy of cancer by lycopene.* Cancer letters, 2008. **269**(2): p. 339-351.
74. Koul, A., et al., *Lycopene enriched tomato extract suppresses chemically induced skin tumorigenesis in mice.* Int J Vitam Nutr Res, 2020. **90**(5-6): p. 493-513.
75. Tripathi, R., R. Shalini, and R.K. Singh, *7 - Prophyletic origin of algae as potential repository of anticancer compounds*, in *Evolutionary Diversity as a Source for Anticancer Molecules*, A.K. Srivastava, et al., Editors. 2021, Academic Press. p. 155-189.
76. Kumar, S.R., M. Hosokawa, and K. Miyashita, *Fucoxanthin: a marine carotenoid exerting anti-cancer effects by affecting multiple mechanisms.* Marine drugs, 2013. **11**(12): p. 5130-5147.
77. Satomi, Y., *Antitumor and Cancer-preventative Function of Fucoxanthin: A Marine Carotenoid.* Anticancer Res, 2017. **37**(4): p. 1557-1562.
78. Kotake-Nara, E., M. Terasaki, and A. Nagao, *Characterization of apoptosis induced by fucoxanthin in human promyelocytic leukemia cells.* Biosci Biotechnol Biochem, 2005. **69**(1): p. 224-7.
79. Examine.com. *Curcumin*. 2015; Available from: https://examine.com/supplements/curcumin/.
80. Sa, G. and T. Das, *Anti cancer effects of curcumin: cycle of life and death.* Cell division, 2008. **3**: p. 14-14.
81. Wilken, R., et al., *Curcumin: A review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma.* Molecular cancer, 2011. **10**: p. 12-12.
82. Phillips, J.M., et al., *Curcumin inhibits skin squamous cell carcinoma tumor growth in vivo.* Otolaryngol Head Neck Surg, 2011. **145**(1): p. 58-63.

83. Arbiser, J.L., et al., *Curcumin is an in vivo inhibitor of angiogenesis.* Molecular medicine (Cambridge, Mass.), 1998. **4**(6): p. 376-383.
84. WebMD. *Beta-Carotene - Uses, Side Effects, and More*. 2022; Available from: https://www.webmd.com/vitamins/ai/ingredientmono-999/beta-carotene.
85. Foundation, S.C. *Can Your Diet Help Prevent Skin Cancer?* 2017; Available from: https://www.skincancer.org/blog/can-your-diet-help-prevent-skin-cancer/.
86. Kim, J., et al., *Association of Vitamin A Intake With Cutaneous Squamous Cell Carcinoma Risk in the United States.* JAMA Dermatology, 2019. **155**(11): p. 12601268.
87. Kune, G.A., et al., *Diet, alcohol, smoking, serum beta-carotene, and vitamin A in male nonmelanocytic skin cancer patients and controls.* Nutr Cancer, 1992. **18**(3): p. 237-44.
88. Green, A., et al., *Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial.* Lancet, 1999. **354**(9180): p. 723-9.
89. Health, N.I.o., *Vitamin A and Carotenoids.* 2022.
90. Plus, M., *Vitamin A.* 2021.
91. Sinai, M., *Vitamin A (Retinol)* 2021.
92. Zasada, M. and E. Budzisz, *Retinoids: active molecules influencing skin structure formation in cosmetic and dermatological treatments.* Postepy dermatologii i alergologii, 2019. **36**(4): p. 392-397.
93. Doctors, S., *Vitamin A to Help Lower Skin Cancer Risk*, in *Sun Doctors*. 2022.
94. Health, N.I.o. *Vitamin C.* 2021; Available from: https://ods.od.nih.gov/factsheets/Vitaminc-Healthprofessional/.
95. Lewis Cantley, J.Y. *Intravenous High-Dose Vitamin C in Cancer Therapy* 2020; Available from: https://www.cancer.gov/research/key-initiatives/ras/rascentral/blog/2020/yun-cantley-vitamin-c.
96. Yang, G., et al., *Vitamin C at high concentrations induces cytotoxicity in malignant melanoma but promotes tumor growth at low concentrations.* Mol Carcinog, 2017. **56**(8): p. 1965-1976.
97. Heymann, W.R. *Vitamin C as treatment of basal cell carcinoma: Is it fruitful?* 2016; Available from: https://www.aad.org/dw/dw-insights-and-inquiries/medicaldermatology/vitamin-c-as-treatment-of-basal-cell-carcinoma-is-it-fruitful.
98. Chen, X.-Y., et al., *Vitamin C induces human melanoma A375 cell apoptosis via Bax- and Bcl-2-mediated mitochondrial pathways.* Oncology letters, 2019. **18**(4): p. 3880-3886.
99. Lisse, T.S. and M. Hewison, *Vitamin D: a new player in the world of mTOR signaling.* Cell cycle (Georgetown, Tex.), 2011. **10**(12): p. 1888-1889.

100. Ross AC, T.C., Yaktine AL, et al., *Dietary Reference Intakes for Vitamin D and Calcium.* National Library of Medicine, 2011.
101. Quigley, M., et al., *Vitamin D Modulation of Mitochondrial Oxidative Metabolism and mTOR Enforces Stress Adaptations and Anticancer Responses.* JBMR plus, 2021. **6**(1): p. e10572-e10572.
102. Vishlaghi, N. and T.S. Lisse, *Exploring vitamin D signalling within skin cancer.* Clin Endocrinol (Oxf), 2020. **92**(4): p. 273-281.
103. D'Orazio, J., et al., *UV radiation and the skin.* International journal of molecular sciences, 2013. **14**(6): p. 12222-12248.
104. Moan, J. and A.C. Porojnicu, *[The photobiology of vitamin D--a topic of renewed focus].* Tidsskr Nor Laegeforen, 2006. **126**(8): p. 1048-52.
105. Holick, M.F., E. Smith, and S. Pincus, *Skin as the site of vitamin D synthesis and target tissue for 1,25-dihydroxyvitamin D3. Use of calcitriol (1,25dihydroxyvitamin D3) for treatment of psoriasis.* Arch Dermatol, 1987. **123**(12): p. 1677-1683a.
106. Sizar O, K.S., Goyal A, et al. *Vitamin D Deficiency*. National Library of Medicine 2022; Available from: https://www.ncbi.nlm.nih.gov/books/NBK532266/.
107. Information, N.C.f.B. *Sulforaphane*. 2022; Available from: https://pubchem.ncbi.nlm.nih.gov/compound/sulforaphane.
108. Alyoussef, A. and M. Taha, *Antitumor activity of sulforaphane in mice model of skin cancer via blocking sulfatase-2.* Exp Dermatol, 2019. **28**(1): p. 28-34.
109. Xu, C., et al., *Inhibition of 7,12-dimethylbenz(a)anthracene-induced skin tumorigenesis in C57BL/6 mice by sulforaphane is mediated by nuclear factor E2related factor 2.* Cancer Res, 2006. **66**(16): p. 8293-6.
110. Talalay, P., et al., *Sulforaphane mobilizes cellular defenses that protect skin against damage by UV radiation.* Proceedings of the National Academy of Sciences of the United States of America, 2007. **104**(44): p. 17500-17505.
111. Dinkova-Kostova, A.T., et al., *KEAP1 and Done? Targeting the NRF2 Pathway with Sulforaphane.* Trends in food science & technology, 2017. **69**(Pt B): p. 257269.
112. MD, W. *Resveratrol - Uses, Side Effects, And More*. 2022; Available from: https://www.webmd.com/vitamins/ai/ingredientmono-307/resveratrol.
113. Ko, J.-H., et al., *The Role of Resveratrol in Cancer Therapy.* International journal of molecular sciences, 2017. **18**(12): p. 2589.
114. Athar, M., et al., *Resveratrol: a review of preclinical studies for human cancer prevention.* Toxicology and applied pharmacology, 2007. **224**(3): p. 274-283.
115. Afaq, F., V.M. Adhami, and N. Ahmad, *Prevention of short-term ultraviolet B radiation-mediated damages by resveratrol in SKH-1 hairless mice.* Toxicol Appl Pharmacol, 2003. **186**(1): p. 28-37.

116. Rizeq, B., et al., *The Power of Phytochemicals Combination in Cancer Chemoprevention.* Journal of Cancer, 2020. **11**(15): p. 4521-4533.
117. Iqbal, J., et al., *Potential phytochemicals in the fight against skin cancer: Current landscape and future perspectives.* Biomed Pharmacother, 2019. **109**: p. 13811393.
118. Chinembiri, T.N., et al., *Review of natural compounds for potential skin cancer treatment.* Molecules (Basel, Switzerland), 2014. **19**(8): p. 11679-11721.
119. Team, T.A.C.S.M.a.E.C. *What Are Basal and Squamous Cell Skin Cancers?* 2019; Available from: https://www.cancer.org/cancer/basal-and-squamous-cell-skincancer/about/what-is-basal-and-squamous-cell.html.
120. M, G., et al., *Eco-Friendly Multifunctional Properties of Cochineal and Weld for Simultaneous Dyeing and Finishing of Proteinic Fabrics.* International Journal of Engineering and Technology, 2016. **8**: p. 2246-2253.
121. Chedea, V.S., *Lipoxygenase-Quercetin Interaction: A Kinetic Study Through Biochemical and Spectroscopy Approaches*. 2012: IntechOpen.
122. Linnewiel-Hermoni, K., E. Paran, and T. Wolak, *Chapter 34 - Carotenoid Supplements and Consumption: Implications for Healthy Aging*, in *Molecular Basis of Nutrition and Aging*, M. Malavolta and E. Mocchegiani, Editors. 2016, Academic Press: San Diego. p. 473-489.
123. Mitra, S., et al., *A Review on Curcumin-Loaded Electrospun Nanofibers and their Application in Modern Medicine.* JOM, 2022.
124. time, D. *Retinol or vitamin*. Available from: https://www.dreamstime.com/retinolvitamin-chemical-formula-retinol-vitamin-image155317917.
125. Chowdhury, M., *Determination of amount of Vitamin C (Ascorbic Acid) from supplied commercial tablets by using Iodometric titration*. 2016.
126. Anne Marie Helmenstine, P.D. *Chemical Structures Starting with the Letter V* 2019; Available from: https://www.thoughtco.com/chemical-structures-startingwith-the-letter-v-4071309.
127. Alena Vanduchova, P.A., Eva Anzenbacherova, *Isothiocyanate from Broccoli, Sulforaphane, and Its Properties.* 2019. **22**(2): p. 121-126.