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POTENTIAL NATURAL SKIN CANCER (MELANOMA) TREATMENTS USING FLAVONOIDS: BIOTHERAPEUTIC APPROACHES

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ABSTRACT: There are a variety of treatment options for melanoma, but the high resistance of tumor cells to conventional therapies makes it necessary to develop new anticancer agents that will have decline toxic effects and greater effectiveness, thereby providing an incentive for the development of new treatments that can be used alone or in combination with other drugs. The flavonoids are phenolic phytoconstituents that have been shown to be efficacious in preventing a wide series of cancers, both *in-vitro* assays and in animal models, including in melanoma cells. Flavonoids, like naringenin, quercetin and apigenin, among others, have gained significant attention in recent years due to the fact that they possess a wide range of properties, including anti-inflammatory, antioxidant, and antiviral properties. However, its anti-carcinogenic effect, which affects the control of cell proliferation and cell-cycle sequence, induction of apoptosis, and suppression of tumor angiogenesis, may be the most significant. Although flavonoids have exhibited promising results both *in-vitro* as well as *in-vivo*, there are some concerns regarding their application to biological environments, such as their low solubility in water, their low stability and their low oral bioavailability in biological environments. Some of the limitations of flavonoids' application may be overcome by nanotechnology in which encapsulated antitumor drugs are used as nano carriers. This approach increase the bioavailability, solubility, stability, and allowing for a controlled and prolonged release, resulting in a targeted response, inhibiting the side effects and improving the effectiveness of flavonoids.

INTRODUCTION: In the field of Oncology, the most aggressive and deadliest type of cancer is Melanoma, which is a malignant oncogenic growth that emerges in melanocytes and belongs to the deadliest type's pathological condition in humans.

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At the early stage of melanoma, surgery is the main treatment option available, but as the cancer progresses; it becomes increasingly resistant to the other therapies available.

This leads to a severe prognosis for those diagnosed with advanced melanoma. Depending upon the stage of the cancer, Melanoma is normally treated with a blend of surgery, chemotherapy, immunotherapy and radiotherapy. There are many reasons why the conventional melanoma therapy does not succeed, such as lack of accessibility of

tumor tissues, a lack of specificity, or toxic side effects. It is also possible for tumors to develop drug resistance, which in turn makes it imperative that new pharmacotherapeutic approaches are developed to improve cancer treatment and boost the quality of human life for cancer patients [1, 2].

There are a variety of treatment options for melanoma, but the high resistance of tumor cells to conventional therapies makes it necessary to develop new anticancer agents that will have decline toxic effects and greater effectiveness, thereby providing an incentive for the development of new treatments that can be used alone or in combination with other drugs. Secondary metabolites have a number of molecular mechanisms of action in tumor cells that are already well understood, acting at enzymes and receptors associated with cell proliferation, differentiation, programmed cell death, inflammation, angiogenesis and also metastasis, as well as signal transduction pathways [3, 4].

Pathophysiological Aspects of Skin Cancer (Melanoma): An adipose skin tumour that is caused by melanocytes, the cells that produce melanin, is known as a melanoma. Melanomas normally occur within the skin but are occasionally found in mucous membranes. They are classified into several subtypes, based on the origin of the cancer, the tumour form, the way that the tumour spreads and infiltrates the possibilities of metastatic spread, etc. It consists of (a) superficial spreading melanoma, which tends to grow outward rather than downward into the skin, (b) nodular melanoma, which tends to grow downward, deeper into the skin is a very slow growing pigmentation on the face, (c) lentigo maligna, also known as Hutchinson's melanotic freckle, and (d) acral lentiginous melanoma, which can occur on the palms or soles of the feet and around a big toenail.

It has been reported that UV radiation from the sun, as well as genetic susceptibility to DNA damage (including faulty DNA repair), are the two most important environmental, genetic factors contributing to the initiation and development of melanoma. There is a strong possibility that precursor lesions, particularly dysplastic nevi and atypical moles, play a critical role in the initiation of melanoma [4–6]. Additionally, the distribution of melanoma across a variety of work forces suggests that occupational threat factors could play a vital role in the aetiology of this cancer based on their association with different types of work. For instance, melanoma incidence is much greater in those who work in the petrochemical, telecommunications, and printing and press industries.

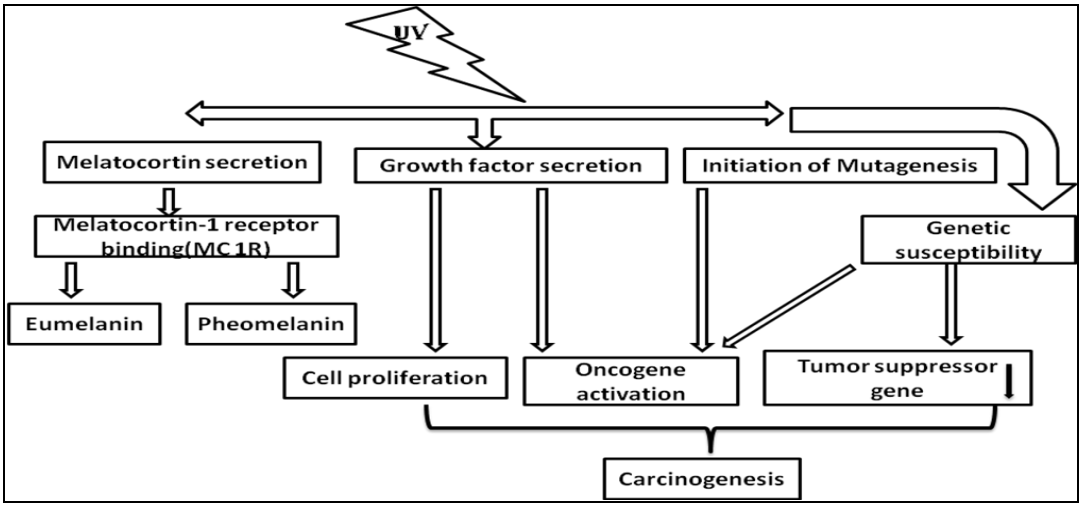

FIG. 1: PATHOPHYSIOLOGICAL MECHANISM OF UV INDUCED MELANOMAS

The growth and amplification of atypical melanocytes along with an array of other characteristics (self-sufficiency of growth factors, low sensitivity to growth inhibitors, and evasion of cellular apoptosis, limitless replicative potential, sustained angiogenesis, tissue invasion, and metastasis) are the pathogenic characteristics of melanomas. By activating oncogenes or deactivating tumor-suppressor genes by molecular mechanisms including dotted mutations, deletions,

and translocations or epigenetic mechanisms like microRNA expression and promoter methylation, these melanoma pathogenic events can be brought about. Analysis of the gene abnormalities in the genome of melanomas has shown the intricate interplay of signalling pathways. Additionally, genetic instability and the preferential proliferation of cells with advantageous mutations are factors in the progression of melanomas. Genetic predisposition, mutagenesis, and a stifled host immune response are further contributors. The MAPK, PI3K/PTEN/AKT, and MITF signalling pathways are some of the most significant signalling pathways implicated in the pathogenesis of melanoma [7, 8].

Melanocyte proliferation, blood vessel growth, tumour invasion, immune response evasion, and metastasis are all caused by an accumulation of genetic mutations in melanocyte that activate oncogenes, inactivate tumour suppressor genes, and impair DNA repair. Environmental exposure (UV light) plus genetic susceptibility (CDKN2A, CDK4, MC1R, BRAF, p16/ARF genes) is the combination that causes these effects [9].

Current Melanoma Treatment: The disease arenas upon diagnosis the degree of metastases have a direct impact on the treatment options for localised or distant metastatic melanoma. Chemotherapies, immunomodulatory medicines, serine/threonine protein kinase (BRAF) inhibitors, mitogen-activated protein kinase (MEK) inhibitors, and most recently vaccinations have all been employed as part of the treatment. Surgery, sentinel lymph node dissection, radical lymph node dissection, and isolated limb perfusion are the main treatments for this kind of malignancy [10, 11].

Patients who have developed a resistance to immunotherapy as well as targeted therapy may now be treated with chemotherapy as a second or third option. By expressing substances with immunosuppressive properties like transforming growth factor-beta (TGF-), vascular endothelial growth factor (VEGF), interleukin-2 (IL-2), as well as by inducing resistance to apoptosis, tumor cells may evade the immune system's attack. The cytotoxic T-lymphocyte-associated protein 4 and programmed cell death protein 1 (PD-1) are two additional cell surface receptors that are expressed by melanoma cells and serve as barriers to immune system responses. The anti-CTLA-4 monoclonal antibody ipilimumab, as well as the anti-PD-1 receptor monoclonal antibodies nivolumab and pembrolizumab, prevent the immune responses suppression by inhibitory ligands. Therefore, the primary goals of immunotherapy are to elicit an immunological response by upregulating tumor-inhibitory T cells, immunostimulation of IL-2, and suppression of immune regulatory points [12–14].

Targeted treatments, such as BRAF gene and also MEK inhibitors, have also been used in the treatment of melanoma in addition to the immunological strategy. The mitogen-activated protein kinase and also signal-regulated kinase (MAPK/ERK) signaling system, which controls cell proliferation, differentiation, and cell cycle progression, is regulated by the BRAF gene, which encodes the B-raf protein. BRAF kinase inhibitors such as vemurafenib and also dabrafenib were created as a result of the finding that BRAF was mutated in roughly half of melanomas [15].

Analysis of all the chosen publications revealed that at least 97 flavonoids have already been studied *in-vitro* or *in-vivo* models for the treatment of melanoma. The fact that the majority of bioactive flavonoids in the world's natural and manmade goods are flavones (38%), flavonols (17.5%) and also isoflavonoids (17.5%) piqued the interest of numerous research organizations [8, 16].

Anti-Melanoma Bio-Activity of Apigenin: Apigenin (4’,5,7,-trihydroxyflavone) is a dietary flavonoid that is typically found in many fruits, vegetables, and medicinal plants. It is nonmutagenic and low in toxicity. This flavone has a wide range of antiproliferative effects on several cancer cell types, including melanoma. Recent research has shown that apigenin suppresses cell proliferation in malignant human melanoma cell lines by arresting the cell cycle and inducing apoptosis.

Additionally, it shown that treating A375 and A2058 human melanoma cells with 50 M apigenin drastically decreased the percentages of viable cells. Apigenin treatment for 24 hours also reduced the quantity of human melanoma cells in a dose-dependent manner.

Anti-Melanoma Bio-Activity of Diosmin: Diosmin (glycosylated flavonoid) that is frequently utilised as an active ingredient in many pharmaceutical products, mostly for the treatment of cardiovascular disorders. Due to its venotonic and vasoprotector qualities, diosmin is used to treat venous insufficiency. In addition, it regulates the activity of various enzymes, including cyclooxygenases and cytochrome P450 proteins, and functions as an antioxidant, anti-inflammatory and anti-mutagenic molecule. Diosmin's anticancer properties have also been researched, which is interesting because it suggests that this flavonoid has a wide range of pharmacological activity. As used an experimental model of B16F10 melanoma cell-induced pulmonary metastasis to compare the effects of three distinct flavonoids (tangeretin, rutin, and diosmin). Treatment with diosmin led to the largest (52% reduction) in the number of metastatic nodules. The implantation, growth, and invasion indices for diosmin also showed a significant decline (79.40, 67.44, and 45.23%, respectively).

Anti-Melanoma Bioactivity of Fisetin: Many fruits and vegetables, including strawberries, apples, persimmons, kiwis, onions, and cucumbers, contain the flavonol known as fisetin (3,3’,4’.7-tetrahydroxyflavone). This flavonoid has demonstrated a significant neuroprotective impact, supporting memory and cognition functions and minimising behavioural impairments. Fisetin's impact on anticancer therapy has also been researched recently. At 24 and 48 hours after treatment, the results of the investigation showed that the IC_{50} values against the A375 human melanoma cell line were 38.1 and 20.3 M. Fisetin has been shown to cause apoptosis in melanoma cells in a later investigation. Preliminary findings revealed that apoptosis is the main mechanism by which fisetin suppresses the proliferation of melanoma cells. The effectiveness of fisetin in the production of apoptosis varied with cell type. Upregulation of ER stress indicators such as IRE1a, XBP1s, ATF4, and GRP78 is one of the potential processes at play.

Anti-Melanoma Bioactivity of Luteolin: Typical flavones like luteolin can be found in a wide variety of plants, including fruits, vegetables and therapeutic herbs. This flavonoid has the potential to treat and prevent cancer. In a preliminary test, it was observed that luteolin exhibited substantial cytotoxicity against the human melanoma cell line A375, with an IC50 value of 115.1 M. This knowledge is important to the treatment of melanoma. By interfering with cellular integrity, luteolin also inhibited colony expansion and triggered apoptosis in a dose and time-dependent manner. Lutein appears to inhibit cell proliferation and promote cell cycle arrest and apoptosis in human melanoma cells by increasing the proportion of cells in the G0/G1 phase for A375 cells after 24 hours of treatment. A similar conclusion was found, and it was noted that the antiproliferative effects of luteolin on OCM-1 human melanoma cells were regulated by the regulation of the cyclin dependent kinases CDK2 and CDK1. In a recent study, ER stress was discovered to be responsible for luteolin's inhibitory effect on melanoma cell proliferation. In this setting, luteolin boosted the production of proteins involved in ER stress, including cleaved caspase 12, activating transcription factor (ATF) 6, CCAAT/enhancer-binding protein homologous protein (CHOP), and protein kinase RNA-like ER kinase. Additionally, luteolin elevated the quantity of intracellular ROS, which produced ER stress and ROS-mediated apoptosis, suggesting that luteolin causes ER stress through triggering apoptosis.

Lutein's anticancer potential has also been investigated *in-vivo*. Treatment of mice with luteolin (10 or 20 mg/kg) amelorated metastatic colonisation in the lungs by 50% in experimental metastasis model. Vimentin and 3 integrin expression was decreased in the cancer tissues although E-cadherin expression was elevated. These findings support the use of luteolin as a chemotherapeutic and chemopreventive medication for the treatment of cancer [17].

Anti-Melanoma Bio-Activity of Quercetin: Quercetin a non-carcinogenic dietary flavonoid that has minimal toxic relationships has been demonstrated to exert antioxidant, anti-inflammatory, neuroprotective, and antimelanoma effects. A prelim inary investigation demonstrated that quercetin presents a modest cytotoxic impact on B16F10 murine melanoma cells with an IC_{50} value > 50 μM. However it has been established that quercetin presents a strong antiproliferative

effect on OCM-1 and SK-MEL-2 human melanoma cells, with an IC_{50} value between 4.7 and 19 μM. In these investigations, the scientists demonstrated that the presence of hydroxyl group at the 30 - position of the ring B in quercetin enhances the cytotoxic action and a G1 cell cycle arrest.

Furthermore, mechanistic investigation demonstrated that quercetin suppresses the activation of STAT3 signaling by interfering with STAT3 phosphorylation, and lowering STAT3 nuclear localization. In an animal model, quercetin suppressed murine B16F10 cells lung metastasis, showing that quercetin possesses anticancer potential [18–20].

Flavonoids Mechanistic Function on Pharmaco-therapeutic of Melanoma: In many different cancer types, like(breast, prostate, pancreatic, bladder, lung, and colon cancer) flavonoids have been extensively employed as experimental chemoprevention and chemotherapeutic agents. Epidemiological studies demonstrate an inverse relationship between cancer risk and estimated dietary consumption of total flavonoids (often not specified). There are currently no well-planned trials for the prevention of cancer (including melanoma). In the table below, we list the possible molecular mechanisms by which flavonoids exert their anti-oxidant, anti-inflammatory, immune-modulating, anti-proliferative, anti-angiogenesis; induce apoptosis, and potential epigenetic modification effects. The majority of these studies were conducted in vitro a few in mice and some were epidemiological annotations [21–24].

Flavonoids like Reactive Oxygen Species (ROS) Scavenger for Melanoma: Multiple research investigations have shown that many flavonoids are strong antioxidants, suggesting that they could be useful as reactive oxygen species scavengers. Flavonoids appear to act as protective agents in situations when there are high levels of ROS, which can lead to a variety of issues such as DNA, lipid, and protein damage as well as abnormal cellular signaling [25–27].

Flavonoids can also target mitochondria and ROS-producing enzymes, however published studies indicate that flavonoids can act as ROS scavengers or ROS stimulators. Apigenin directly attacked the mitochondrial oxidative phosphorylation pathway in A375 cells, disrupted it, and increased ROS levels, which caused cell death. Similarly, quercetin enhanced ROS levels in DB-1 melanoma cells via reducing bio-reduction capability, namely the glutathione-S transferase and NQO1 levels, whereas baicalein also elevated ROS in B16 cells, potentially via 12-lipoxygenase. On the other hand, luteolin directly decreased cellular ROS levels in B16 cells and dose-dependently inhibited xanthine oxidase activity.

Flavonoids Role in (Anti-Inflammation, Immune Modulation) in Melanoma: Plenty of evidence exists that immune suppression and inflammation play significant roles in the aetiology, development, and even prognosis of melanoma: 1) Skin immune suppression is caused by Ultra-Violet (UV) radiation, which is a key environmental risk factor; 2) melanoma tumours have significant immune cell infiltration; and 3) BRAF inhibitor-mediated immunosuppression contributes to treatment failure. Additionally, oxidative stress, which is significantly enhanced in melanoma, demonstrates an intrinsic link with inflammation [28]. The anti-inflammatory characteristics of flavonoids in preclinical studies have indicated a potentially significant impact on the aetiology, prevention, and treatment outcomes of melanoma. In melanoma and skin tissues, flavonoids control inflammatory responses through a few important mediators, in brief: Nitric oxidases, primarily iNOS and nNOS, NFB, STAT3, and members of the AP-1 family of transcriptional factors.

AP-1 can be blocked by luteolin, quercetin, and apigenin. AP-1 and NF-B have the ability to up-regulate the expression of cytokines like IL-8. Luteolin was found to encourage STAT3's proteasome-mediated degradation, which in turn prevented cytokines like IL6 and IL10 from sending inflammatory signals [4, 29].

Flavonoids like Anti-Proliferative, Apoptotic Induction and Anti-Metastatic Activities: Through the HGF/SF-Met signaling, mitogen-activated protein kinases pathway, cell cycle regulation, differentiation induction, and PI3K-AKT pathway, flavonoids have anti-proliferative and anti-apoptotic actions.

Various flavonoids have various impacts on the wide variety of cellular targets that they target; similar to how they function in melanogenesis. In decreasing order of efficiency, flavonoids EGCG, apigenin, and quercetin reduced the growth of xenografted B16-BL6 murine melanoma, with the last two substances having effects resembling those of Tamoxifen [13, 30].

Molecular Docking, Molecular Dynamics Simulation: Molecular Mechanism of Flavonoids Anti-Melanoma: Through the use of network pharmacology, 3D/2D-QSAR, molecular docking, and molecular dynamics (MD) modeling, the molecular mechanism of flavonoids' anti-melanoma activity was investigated. Various flavonoids, including licochalcone B, naringenin, and DL-liquiritigenin, were important anti-melanoma active flavonoids, and Tyr was the main target of anti-melanoma, according to network pharmacology research.

Licochalcone B, licochalcone A, 6-gingerol, retrochalcone, formononetin, licoflavone A, and daidzein were found to be extremely effective compounds in the anti-melanoma activity of flavonoids, according to research using the 2D-QSAR pharmacophore model.

The 3D-QSAR model's findings demonstrated that one hydrophobic group, two hydrogen-bonded donor groups, and one hydrogen-bonded acceptor group made up the ideal flavonoid pharmacophore. According to molecular docking studies, flavonoids' anti-melanoma activity was mostly mediated by the best pharmacophore model created by 3D-QSAR.

Flavonoids had a strong binding affinity for the protein kinase domain of Src, as demonstrated by molecular modeling and surface plasmon resonance imaging. Animal studies showed that prophylactic treatment of flavonoids in both A375 and B16F10 melanoma-bearing mice inhibited melanoma growth and Src/STAT3 signaling [13, 30–32].

CONCLUSION: Flavonoids can be extracted from a variety of foods and herbs, and they have the potential to be highly effective medicinal agents. More *in-vivo* studies and human trials are required to fully understand the therapeutic activity of flavonoids, as there haven't been many (if any) clinical trials to establish the profile of flavonoids and the toxicity curve at the doses needed to prevent or treat cancer in people. Although the intracellular target of each chemical is difficult to identify, their general effectiveness should be highlighted. Because they can simultaneously target numerous different genes, they may lack specificity, yet this may also be the exact source of their functional diversity. Additionally, flavonoids undergo metabolism much like other chemical compounds do, and the metabolites may also function as active ingredients in living organisms, making it even more challenging to pinpoint a specific target. The examination of the clinical utility of nutraceuticals by researchers and the general public should recognize this diversity of action and not be constrained by the "targeted therapy" dogma.

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CONFLICT OF INTEREST: Author M.K. Prajapati and Abhilasha Mittal declare that they have no conflict of interest.

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