Review of selected herbal phytoconstituents for potential melanoma treatment

Bhaskar Kallappa Kurangi¹, Sunil Satyappa Jalalpure¹,2

Abstract:
Malignant melanoma is the most aggressive form of skin cancer, with a high mortality rate. The current chemotherapies have a relatively low success rate due to the development of multidrug resistance and side effects. Hence, there is need of discovering new compounds that are safe and more effective against melanoma to improve the efficiency and to lower the treatment cost for cancer care. Melanoma chemoprevention with natural herbal phytoconstituents is an emerging strategy to prevent, cure, or treat melanoma. This review summarizes the latest research in melanoma chemoprevention and treatment using the herbal phytoconstituents. Relevant mechanisms involved in the pharmacological effects of these phytochemicals are discussed. Phytoconstituents that are discussed in this review are carotenoids, flavonoids, some polyphenols, piperine alkaloid, and sulforaphane having high anticancer potential mostly to be used for the treatment of melanoma.

Keywords:
Anticancer, chemoprevention, melanoma, phytoconstituents

Introduction

Melanoma

Melanoma is the most fatal kind of skin cancer which is a malignant tumor that originates from melanocytes and especially involves the skin [Figure 1]. Apart from the skin, melanomas can also found in the eyes and meninges and on various mucosal surfaces. Usually, melanomas are pigmented and amelanotic. Even the small tumors can have a tendency to metastasize and thus lead to an unfavorable prognosis. The death rate associated with melanoma is 90% which can be related with cutaneous tumors.¹,² Melanoma incidence is going to be increased worldwide in the White populations with excessive sun exposure.³ Malignant melanoma is most common among the White-skinned peoples than Black, Asian, or Hispanic population. The White-skinned people have approximately 10 times greater risk of developing melanoma.⁴ However, in the plantar malignant melanoma, it was found that melanoma incidence is equal in both the White and Black population.⁵ In India, malignant melanoma is not common and its incidence rate is <0.5%.⁶

Ultraviolet irradiation is the most important exogenous factor for melanoma, particularly intermittent sun exposure.⁶ Malignant melanoma is most common among the White-skinned peoples than Black, Asian, or Hispanic population. The White-skinned people have approximately 10 times greater risk of developing melanoma.⁷ However, in the plantar malignant melanoma, it was found that melanoma incidence is equal in both the White and Black population.⁸ In India, malignant melanoma is not common and its incidence rate is <0.5%.⁹

The current clinical approach and therapy selected for cutaneous melanoma are surgery, chemotherapy or immunotherapy, and/or the combination of the two. Unfortunately, attempts made for improving the survival by surgically removing lymph
nodes can result in no overall survival benefits.\textsuperscript{[10]} Other than surgery, there are two major alternatives for the management of melanoma such as chemotherapy and immunotherapy. Although the current chemotherapies have their advantages, they are either not effective enough or cause serious side effects and toxicity. In the randomized experiments to date for melanoma, it has been reported that no single drug or combination of therapies is superior to existing drugs.\textsuperscript{[11]} Therefore, there is need for herbal drugs which can offer improved efficacy over existing chemotherapy, in melanoma therapy.

**Need of natural herbal products**

Development of multidrug resistance and severe adverse effects is the main problem that exists with chemotherapeutic agents. Some of the methods by which melanoma cells can develop resistant to chemotherapeutic agents are drug efflux systems, amplification of drug targets, or changes in drug kinetics.\textsuperscript{[12‑14]} To overcome drug resistance, different strategies have been attempted, such as use of nanoparticles, liposomes, and micellar drug delivery vehicles, with some reported successes.\textsuperscript{[14]} The adverse effects, side effects, and multidrug resistance of cancer chemotherapy can be treated symptomatically, but in some instances, some secondary treatments may be very toxic, which is unacceptable to some cancer patients.\textsuperscript{[15‑17]}

Because of the drawbacks associated with conventional cancer chemotherapies, interest has been grown for natural therapies. Different phytochemical compounds obtained from the extracts of plant roots, bulbs, barks, leaves, stems, and others have shown promising potential as anticancer drugs or for serving as lead compounds in the synthesis of new drugs. The main limiting factor for natural products and traditional medicines is the different preparation method. Apart from that chemical composition, dosage determination, dose adjustment, and suitable route of administration are also important factors for the herbal medicines. Although much research on the compounds of natural origin is required to produce new drug products for which research, specifically aimed at naturally derived medicines to optimize dosages for the intended route of administration and to design the most effective dosage forms, has become essential.\textsuperscript{[18]}

**Phytoconstituents Showing Activity for Melanoma**

Phytoconstituents exert different types of immunomodulatory, anti-inflammatory, and antioxidant properties, but generally, they have the highest potential of exerting chemopreventive action in melanoma.\textsuperscript{[19]} Number of research has been done to find out the correlation between antioxidant properties and anticancer activity of these phytoconstituents. No strong evidence has been found related with such a correlation still, but the antioxidant potential of a phytoconstituent is being regarded as an indication for potential anticancer activity.\textsuperscript{[20,21]} Phytoconstituents such as carotenoids, flavonoids, and terpenoids having high anticancer potential can be used for the treatment of melanoma [Figure 2].\textsuperscript{[22‑24]}

**Flavonoids**

Flavonoids are pigmentary compounds which exist in plants. Structurally, flavonoids contain two benzene rings which are connected through a linear carbon chain and an aromatic chromophore.\textsuperscript{[25]} Flavonoids include flavones, flavanones, isoflavones, anthocyanins, and flavan-3-ols (catechins). Figure 3 describes the chemical structures of some flavonoids which exhibit anticancer activities.

**Epigallocatechin-3-gallate**

The catechin epigallocatechin-3-gallate (EGCG) is one of the main flavonoid compounds found in green tea which has been received enormous pharmacological attention because of its potential benefits to health. EGCG possess anti-inflammatory, antioxidant, antimutagenic, and anticarcinogenic properties.\textsuperscript{[26‑28]}

It has been reported that EGCG has the capacity to induce apoptosis and cell cycle arrest in melanoma cells, either alone or in combination with vorinostat in vitro.\textsuperscript{[29,30]} For the melanoma treatment, a combination strategy with interferon has shown synergistic antiproliferative effects in both in vitro and in vivo studies.\textsuperscript{[31]} Different mechanisms by which EGCG has shown effects include upregulation of Bcl-2-associated X protein, downregulation of apoptosis-inhibiting proteins, cell survival-promoting proteins, a pro-apoptosis protein, activation of caspases-3, -7, and -9, and through the induction of tumor suppressor proteins.\textsuperscript{[32,33]} EGCG showed pro-apoptotic activity, selective toward melanoma cells and not toward the normal melanocytes.\textsuperscript{[33]} Development of EGCG into a practical therapeutic agent may require an interdisciplinary approach to modify EGCG.
structure and increase its potency and pharmacokinetic properties.

**Quercetin**
Quercetin is the most abundant flavonol present in the human diet and in plants in different glycosidic forms, such as galactosides, rhamnosides, arabinosides, or glucosides. The derivatives of quercetin accounts for 60% of the total flavonoids ingested daily and are the most abundant and important dietary flavonoids present in the human diet. The quercetin derivatives are commonly found in many fruits and vegetables, such as red onions, apples, berries, parsley, olive oil, cocoa, citrus fruits, tea, and red wine.

The mechanism by which quercetin had shown activity against melanoma at low concentrations by affecting cell viability and at higher concentrations by inducing apoptosis. It was reported that in murine melanoma cells, quercetin induced apoptosis by diminishing the expression of B-cell lymphoma 2 and increasing the effectiveness of caspase-3 activity. The recent study has reported that the quercetin activity for melanoma may be due to inhibitory effects on signal transducer and activator of transcription 3, which is an oncogenic protein. Overall quercetin could be used to take advantage of tyrosinase activity in melanoma treatment with minimum additional side effects related with it. However, dietary intake would be suitable in the development of preventative approaches, while systems including nanoparticles or any other nanoformulation will be required to achieve the best effective quercetin concentrations for therapeutic approaches.

**Kaempferol**
Kaempferol, a natural flavonol compound belonging to flavonoids category, occurs mostly in a variety of plants and plant-derived food products. Kaempferol is abundantly available in tea, broccoli, beans, strawberries, and apples.

Kaempferol acts in the different mechanisms for regulation of cancer cells. It has been reported that kaempferol is a potent promoter of apoptosis and also it modifies a host of cellular signaling pathways such as inhibiting cell proliferation. Compared to standard
chemotherapeutic drugs, kaempferol is much less toxic to normal cells. A study has shown that kaempferol blocks choroidal melanoma cell cycle progression in the G2/M phase. For transdermal delivery, the kaempferol submicron emulsion systems has been developed, and it was found that because of emulsion systems, there was significant influence on the flux, the amount of drug deposition in skin and lag time. The synergistic activity along with quercetin has been shown in melanogenesis inhibition. Moreover, they were considered as good blockers of enzyme activity, especially in hyperpigmentation.

**Daidzein**

Daidzein is an isoflavone, which is a hormone-like substance found exclusively in soybeans and other legumes. It is highly soluble in alkaline environments and is part of a group of compounds, called phytoestrogens.

Daidzein has shown some effective photo-protection potential in the skin by topical application. Daidzein and genistein have been investigated to produce synergistic inhibitive effect on the metastatic melanoma cells (murine K1735M2).

**Apigenin**

Apigenin is a naturally occurring product belonging to the flavonoids category which is anaglycone of several naturally occurring glycosides. Apigenin is mostly found in celery, oranges, tea, parsley, thyme, and onions.

The anticancer activities of apigenin have been observed in vitro in the melanoma cell lines (MELs-28). The different mechanisms by which apigenin exerts action include inducing cell cycle arrest in the G2/M phase, upregulating tumor necrosis factor receptor (TNF-Receptor), and the TNF-related apoptosis-inducing ligand receptor apoptotic pathway. The combinations of all these actions result into chemoprotective effects of apigenin. Subsequent studies on apigenin has shown antimalanoma effects, which includes inhibition metastasis of melanoma. Along with quercetin, there is inhibition of melanoma growth and invasive and metastatic melanoma.

**Rutin**

Rutin is the glycoside which is the combination of quercetin flavonol and the rutinoside disaccharide. It occurs in a wide variety of plants such as passion flower, buckwheat, tea, and apple. It is one of the vital nutritional components of food stuff.

It has demonstrated a number of pharmacological activities, including antioxidant, cytoprotective, vasoprotective, anticarcinogenic, neuroprotective, and cardioprotective activities. One study has reported that rutin inhibited the growth and tumor weight of B16 melanoma as well as melanin content in C57BL/6 mice.

**Carotenoids**

Carotenoids are a class of >750 naturally occurring fat-soluble pigments commonly found in plants, algae, and photosynthetic bacteria. The carotenoids containing the structure such as distinctive conjugated double bond which acts as a light-absorbing chromophore and that imparts yellow, orange, or red color to vegetables, oranges, and other food products. Carotenoids are divided into two classes, such as xanthophylls and carotenes. Figure 4 describes the chemical structures of some carotenoids which exhibit anticancer activities, especially against melanoma.

**Lycopene**

The red color to fruits and vegetables is imparted by a natural pigment which is lycopene. Lycopene is found in watermelons, pink grapefruits, apricots, and pink guavas. It is found in particularly high amounts in tomatoes and tomato products.

Lycopene is one of the most effective carotenes for oxidative stress reduction. It should be considered as an excellent additive to the diets of patients which are at high risk for melanoma. Studies have shown that lycopene inhibits platelet-derived growth factor-BB, which in turn reduces melanoma cell-induced fibroblast migration and signaling transduction. Hence, this explains that lycopene bears the antitumor properties.

**Fucoxanthin**

Fucoxanthin is an orange-colored pigment, together with chlorophylls a, c and β-carotene which are to be found in chromophya, brown seaweeds, and diatoms.

Fucoxanthin exerts anticancer effects such as reduced tumor incidences, cell cycle arrest, induction of apoptosis, inhibition of proliferation, and inhibition of metastasis. The in vitro and in vivo study has shown that fucoxanthin inhibits the growth of B16F10 melanoma cells. In SK-MEL-28 malignant MEL-28 study, the anticancer effect of fucoxanthin has also been reported. Fucoxanthin also shown the activity against metastatic melanoma by suppressing murine melanoma cells, by downregulation of proteins involved in cell migration, cell interaction, and cell adhesion.

**β-Carotene**

β-Carotene is an organic, abundantly found in plants and fruits. β-Carotene is a pigment which has strong red-orange color. In nature, β-carotene is a precursor to vitamin A. β-Carotene was described as an antioxidant that protected against cancer, heart disease, macular degeneration, and aging.
The in vitro study in melanoma cells reported that β-carotene is able to induce apoptosis by activating caspases-3, -8, and -9 through caspase cascade.[70] It was reported that the diet high in β-carotene may be related to a decreased melanoma risk.[71,72]

**Alkaloid**
Alkaloids are a group of naturally occurring nitrogenous chemical compounds found in plants, typically insoluble in water. The different organisms such as bacteria, fungi, plants, and animals are the main source of the alkaloids. Alkaloids are exerting different pharmacological actions such as antimalarial, antiasthma, anticancer, vasodilatory, antiarrhythmic, analgesic, antibacterial, and antihyperglycemic activities.[73] Berberine, cryptolepine, and vinca alkaloids have been shown activity for melanoma. In this present review, the alkaloid discussed for antimelanoma activity is piperine.[74‑76]

**Piperine**
Piperine is an alkaloid found in *Piper nigrum* and *Piper longum*. It exhibits wide variety of biological actions such as anti-inflammatory, antioxidant, antiarthritic and antidepressant effects Figure 5 shows chemical structure of piperine.[77,78]

Piperine inhibits CYP3A4 and P-glycoprotein by which bioavailability of other drugs can be enhanced.[79] Curcumin has different stability problems.[80] Along with curcumin, administration of piperine increases bioavailability of curcumin.[79] Clinical trials are also being conducted to evaluate the effect of piperine in enhancing the bioavailability of other phytoconstituents. The antiproliferative effects of piperine in murine as well as in human melanoma cells were studied. The studies have reported that growth inhibitory effects of piperine were mediated by apoptosis and cell cycle arrest of both the cell lines, i.e., SK-MEL-28 and B16 F0 cells in G1 phase.[81]

**Polyphenol**
Polyphenols are mainly natural but also synthetic or semisynthetic, organic chemicals characterized by the presence of large multiples of phenol structural rings. There are over 8000 identified polyphenols compounds found most abundantly in whole foods such as dried spices, fruits, vegetables, red wine, and cocoa, tea, wine, and chocolates.[82] Polyphenol plays an important role in the prevention and in reduction of progression of diseases such as diabetes, cardiovascular and neurodegenerative diseases, and cancer. Figure 6 shows
the chemical structure of selected polyphenols having antitumor activity.\[^{[8]}\]

**Ellagic acid**

Ellagic acid is a fused four-ring polyphenol. Ellagic acid is present in many red fruits and berries, including raspberries, strawberries, blackberries, cranberries, pomegranate, and some nuts including pecans and walnuts.

It possesses antifibrotic and antioxidant properties and also exhibits \textit{in vitro} antitumor properties against various cancer cells.\[^{[84,85]}\] Ellagic acid had shown apoptosis induction property in human melanoma cells.\[^{[86]}\] Ellagic acid is thought to suppress melanogenesis by reacting with activated melanocytes and without injuring cells.\[^{[87]}\]

**Resveratrol**

Resveratrol is a nutraceutical which has exciting pharmacological potential and because of this recently attracted a lot of research attention. It is a phytoalexin compound found in many plants such as grapes, peanuts, and berries. Resveratrol is a model stilbene having cardioprotection, chemoprevention, and antitumor activities.\[^{[88]}\]

Resveratrol has been investigated as an anticancer agent. In doxorubicin-resistant murine melanoma cells, the potency of resveratrol has been demonstrated by inducing apoptosis and inhibiting the growth of melanoma tumors in mice.\[^{[89]}\] The \textit{in vitro} study had shown that combination with temozolomide act as an effective cytotoxic agent against melanoma cells.\[^{[90]}\] Due to its low bioavailability, the \textit{in vivo} anticancer effects of resveratrol are strongly limited.\[^{[91]}\] Hence, approaches are to be done to increase its bioavailability either by bioenhancer or by nanotechnology approaches. The study had shown that resveratrol sensitizes melanoma cells to interleukin-2 immunotherapy which had caused induced cell death.\[^{[92]}\]

**Indoles and glucosinolates**

Glucosinolates are a group of secondary products found in plants of the family \textit{Cruciferae}. On enzymatic hydrolysis, they give rise to volatile, pungent, and physiologically active compounds which have antifungal, antibacterial, bioherbicidal, biopesticidal, antioxidant, antimutagenic, and anticarcinogenic activity. Recently, indole glucosinolates are attracting attention because of its properties. On hydrolysis either by chemical or enzymatic, the indole glucosinolates give the different involatile indole compounds which have anticarcinogenic activity.\[^{[93]}\]

**Sulforaphane**

Sulforaphane is an isothiocyanate found especially in broccoli sprouts, Chinese kale, cabbage, and watercress. It prevents or delays preneoplastic lesions in mouse skin. Sulforaphane has therapeutic activity in tumor cell cultures, carcinogen-induced cancer models, and genetic animal cancer models.\[^{[84,85]}\] The mechanisms by which sulforaphane exerts anticancer activity by suppressing various critical hallmarks of cancer, such as cell growth and proliferation, apoptosis, invasion, and migration.\[^{[94]}\]

In combination with quercetin, sulforaphane inhibits the proliferation and migration of melanoma (B16F10) cells more effectively than either compound used alone. This combined effect was predominantly due to a decrease in matrix metalloproteinases expression in the mouse tumors.\[^{[95]}\]

The sulforaphane has shown antimetastatic activity in murine melanoma model with \textit{in vivo} study by which it will be helpful in cancer immunotherapy.\[^{[96]}\]

**Pharmaceutical Developmental Challenges and Opportunities**

Traditional use of natural herbal phytoconstituents in melanoma treatment is relatively cheap due to the availability of plants and the simple methods used in formulation development. However, commercialization of natural compounds for cancer treatment, i.e., for melanoma, may result in declining of natural resources and problems with producing a consistent quality of adulteration. Hence, most naturally derived medicinal compounds are eventually manufactured by either semisynthetically or fermentation. For commercial use, these are formulated into an appropriate dosage form by which cost of the products get increased. As cancer chemoprevention and treatment using natural phytoconstituents have been such an attractive approach, further efforts are very justifiable to thoroughly understand their potencies, pharmacokinetic performances, pharmacodynamic responses, metabolisms, toxicities, drug–drug interactions, polymorphisms, and then formulations, stabilities and degradations, and dosage regimens. Lots of scientific research are to be needed to evaluate and optimize the herbal phytochemical products for safe and more effective human use. Phytochemical products should be formulated by a novel method of nanotechnology. The drawbacks related to phytoconstituents such as poor pharmacokinetic properties, targetability, and poor bioavailability of herbal phytoconstituents, for which nanotechnology should be introduced.

**Conclusion**

From this review, it has become clear that herbal phytoconstituents can play a major role in future melanoma treatments. This article has summarized some...
selected herbal phytoconstituents such as carotenoids, flavonoids, some polyphenols, piperine alkaloid, and sulforaphane which have been studied for their possible antimelanoma activity. Antimelanoma activities of phytoconstituents can be ascribed to a distinct phytochemical or to a combination of the effects of different phytochemicals. Most of the phytoconstituents have shown both in vitro and in vivo activity for melanoma. Hence, natural phytoconstituents have been and will continue to be a promising and active source for the drug discovery in the treatment of melanoma.

Financial support and sponsorship Nil.

Conflicts of interest There are no conflicts of interest.

References

1. Eggermont AM, Spatz A, Robert C. Cutaneous melanoma. Lancet 2014;383:816-27.
2. Garbe C, Peris K, Hauchild A, Saig P, Middleton M, Spatz A, et al. Diagnosis and treatment of melanoma: European consensus-based interdisciplinary guideline. Eur J Cancer 2010;46:270-83.
3. American Cancer Society. Cancer Facts & Figures 2016. Atlanta: American Cancer Society; 2016. p. 1-66.
4. WHO. Sunbeds, Tanning and UV Exposure. Fact Sheet No. 287. Interim Revision. WHO Media centre who.int/mediacentre/.../print.html: World Health Organization; 2010.
5. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2013;136:E359-86.
6. Tsao H, Atkins MB, Sober AJ. Management of cutaneous melanoma. N Engl J Med 2004;351:998-1012.
7. Ries LA, Wingo PA, Miller DS, Howe HL, Weir HK, Rosenberg HM, et al. The annual report to the nation on the status of cancer, 1973-1997, with a special section on colorectal cancer. Cancer 2000;88:2398-424.
8. Stevens NG, Liff JM, Weiss NS. Plantar melanoma: Is the incidence of melanoma of the sole of the foot really higher in blacks than whites? Int J Cancer 1990;45:691-3.
9. Boyle P, Maisonneuve P, Dore JF. Epidemiology of malignant melanoma. Br Med Bull 1995;51:523-47.
10. Thomas JM. Sentinel-node biopsy in melanoma. N Engl J Med 2007;356:418.
11. Anderson CM, Buzaid AC, Legha SS. Systemic treatments for cutaneous advanced melanoma. Oncology (Williston Park) 1995;9:1149-58.
12. Iyer AK, Singh A, Ganta S, Amiji MM. Role of integrated cancer nanomedicine in overcoming drug resistance. Adv Drug Deliv Rev 2013;65:1784-802.
13. Kunjachan S, Rychlik B, Storm G, Kiessling F, Lammers T. Multidrug resistance: Physiological principles and nanomedical solutions. Adv Drug Deliv Rev 2013;65:1852-65.
14. Markman JL, Rekechentukay A, Holler E, Ljubimova JY. Nanomedicine therapeutic approaches to overcome cancer drug resistance. Adv Drug Deliv Rev 2013;65:1866-79.
15. Alifrangis C, Koizia L, Rozario A, Rodney S, Harrington M, Somerville C, et al. The experiences of cancer patients. QJM 2011;104:1075-81.
16. Slevin ML, Stubbs L, Plant HJ, Wilson P, Gregory WM, Armes PJ, et al. Attitudes to chemotherapy: Comparing views of patients with cancer with those of doctors, nurses, and general public. BMJ 1990;300:1458-60.
17. Thornton M, Parry M, Gill P, Mead D, Macbeth F. Hard choices: A qualitative study of influences on the treatment decisions made by advanced lung cancer patients. Int J Palliat Nurs 2011;17:68-74.
18. Cragg GM, Newman DJ. Natural products: A continuing source of novel drug leads. Biochim Biophys Acta 2013;1830:3670-95.
19. Katiyar SK. Green tea prevents non-melanoma skin cancer by enhancing DNA repair. Arch Biochem Biophys 2011;508:152-8.
20. Wang S, Meckling KA, Marcone MF, Kakuda Y, Tsao R. Can phytochemical antioxidant rich foods act as anticancer agents? Food Res Int 2011;44:2545-54.
21. Saeidnia S, Abdollahi M. Antioxidants: Friends or foe in prevention or treatment of cancer: The debate of the century. Toxicol Appl Pharmacol 2013;271:49-63.
22. Batra P, Sharma AK. Anti-cancer potential of flavonoids: Recent trends and future perspectives. 3 Biotech 2013;3:439-59.
23. Kuttan G, Pratheeshkumar P, Manu KA, Kuttan R. Inhibition of tumor progression by naturally occurring terpenoids. Pharm Biol 2011;49:995-1007.
24. Steinmetz KA, Potter JD. Vegetables, fruit, and cancer. II. Mechanisms. Cancer Causes Control 1991;2:427-42.
25. Corcoran MP, McKay DL, Blumberg JB. Flavonoid basics: Chemistry, sources, mechanisms of action, and safety. J Nutr Gerontol Geriatr 2012;31:176-89.
26. Ahmed S, Rahman A, Hasnain A, Lalonde M, Goldberg VM, Haqgi TM, et al. Green tea polyphenol epigallocatechin-3-gallate inhibits the IL-1 beta-induced activity and expression of cyclooxygenase-2 and nitric oxide synthase-2 in human chondrocytes. Free Radic Biol Med 2002;33:1097-105.
27. Ichikawa D, Matsui A, Imai M, Sonoda Y, Kasahara T. Effect of various catechins on the IL-12p40 production by murine peritoneal macrophages and a macrophage cell line, J774.1. Biol Pharm Bull 2004;27:1533-8.
28. Shin HY, Kim SH, Jeong HJ, Kim SY, Shin TY, Um JY, et al. Epigallocatechin-3-gallate inhibits secretion of TNF-alpha, IL-6 and IL-8 through the attenuation of ERK and NF-kappaB in HMC-1 cells. Int Arch Allergy Immunol 2007;142:335-44.
29. Zhang G, Miura Y, Yagasaki K. Induction of apoptosis and cell cycle arrest in cancer cells by in vivo metabolites of teas. Nutr Cancer 2000;39:265-73.
30. Nihal M, Roelke CT, Wood GS. Anti-melanoma effects of vorinostat in combination with polyphenolic antioxidant (−)-epigallocatechin-3-gallate (EGCG). Pharm Res 2010;27:1103-14.
31. Nihal M, Ahsan H, Siddiqui IA, Mukhtar H, Ahmad N, Wood GS. (−)-Epigallocatechin-3-gallate (EGCG) sensitizes melanoma cells to interferon induced growth inhibition in a mouse model of human melanoma. Cell Cycle 2009;8:2057-63.
32. Chung SY, Hong W, Guang XL, Zhihong Y, Fei G, Huanyu J. Review: Cancer prevention by tea: Evidence from laboratory studies. Pharm Res 2011;6:113-22.
33. Nihal M, Ahmad N, Mukhtar H, Wood GS. Anti-proliferative and proapoptotic effects of (−)-epigallocatechin-3-gallate on human melanoma: Possible implications for the chemoprevention of melanoma. Int J Cancer 2005;114:513-21.
34. Erlund M, Linden T, Norlin P, Lehtonen A, Boman G, Sjogren I. Review of the flavonoids quercetin, hesperetin, and naringenin: Dietary sources, bioactivities, bioavailability, and epidemiology. Nutr Res 2004;24:851-74.
35. Hollman PC, van Trijp JM, Mengelers MJ, de Vries JH, Katan MB. Bioavailability of the dietary antioxidant flavonol quercetin in man. Cancer Lett 1997;114:139-40.
36. O’Prey J, Brown J, Fleming J, Harrison PR. Effects of dietary...
flavonoids on major signal transduction pathways in human epithelial cells. Biochem Pharmacol 2003;66:2075-88.

37. Harwood M, Danielewska-Nikli B, Borzellica JF, Flamn GW, Williams GM, Lines TC, et al. A critical review of the data related to the safety of quercetin and lack of evidence of in vivo toxicity, including lack of genotoxic/carcinogenic properties. Food Chem Toxicol 2007;45:2179-205.

38. Spagnuolo C, Russo M, Bilotto S, Tedesco I, Laratta B, Russo GL, et al. Dietary polyphenols in cancer prevention: The example of the flavonoid quercetin in leukemia. Ann N Y Acad Sci 2012;1259:95-103.

39. Rosner K, Röpke C, Pless V, Skovgaard GL. Late type apoptosis and apoptosis free lethal effect of quercetin in human melanoma. Biosci Biotechnol Biochem 2006;70:2169-77.

40. Zhang XM, Chen J, Xia YG, Xu Q. Apoptosis of murine melanoma B16-BL6 cells induced by quercetin targeting mitochondria, inhibiting expression of PKC-alpha and translocating PKC-delta. Cancer Chemother Pharmacol 2005;55:251-62.

41. Cao HH, Tse AK, Kwan HY, Yu H, Cheng CY, Su T, et al. Quercetin exerts anti-melanoma activities and inhibits STAT3 signaling. Biochem Pharmacol 2014;87:424-34.

42. Somerset SM, Johannot L. Dietary flavonoid sources in Australian adults. Nutr Cancer 2008;60:442-9.

43. Ramos S. Effects of dietary flavonoids on apoptotic pathways related to cancer chemoprevention. J Nutr Biochem 2007;18:427-42.

44. Zhang Y, Chen AY, Li M, Chen C, Yao Q, Ginkgo biloba extract kaempferol inhibits cell proliferation and induces apoptosis in pancreatic cancer cells. J Surg Res 2008;148:17-23.

45. Casagrande F, Darbon JM. Effects of structurally related flavonoids on cell cycle progression of human melanoma cells: Regulation of cyclin-dependent kinases CDK2 and CDK1. Biochem Pharmacol 2001;61:1205-15.

46. Chao Y, Huang CT, Fu LT, Huang YB, Tsai YH, Wu PC, et al. The effect of submicron emulsion systems on transdermal delivery of kaempferol. Chem Pharm Bull (Tokyo) 2012;60:1171-5.

47. Taherkhani N, Gheibi N. Inhibitory effects of quercetin and kaempferol as two propolis derived flavonoids on tyrosinase enzyme. Biotechnol Health Sci 2014;1:222-24.

48. Huang ZR, Hung CF, Lin YK, Fang JY. In vitro and in vivo evaluation of topical delivery and potential dermal use of soy isoflavones genistein and daidzein. Int J Pharm 2008;364:36-44.

49. Lin JY, Tournas JA, Burch JA, Monteiro-Riviere NA, Zielinski J. Topical isoflavones provide effective photoprotection to skin. Photodermatol Photoin photomed 2008;24:61-6.

50. Yong Z, Hongzhong X, Feng W, Xuya Y, Chaoyin C, Rongqing Z. Effects of genistein and daidzein on the proliferation, invasion, migration and adhesion of melanoma cells. Isinghua Sci Technol 2020;2:398-403.

51. Shukla S, Gupta S. Apigenin and cancer chemoprevention. In: Watson RR, Freedy VR, editors. Bioactive Foods in Promoting Health: Fruits and Vegetables. London, UK: Elsevier; 2010.

52. Caltagirone S, Rossi C, Poggi A, Ranelletti FO, Natali PG, Brunetti M, et al. Flavonoids apigenin and quercetin inhibit melanoma growth and metastatic potential. Int J Cancer 2000;87:595-600.

53. Piantelli M, Rossi C, Iezzi M, La Sorda R, Iacobelli S, Alberti S, et al. Flavonoids inhibit melanoma lung metastasis by impairing tumor cells endothelium interactions. J Cell Physiol 2006;207:23-9.

54. Harborne JB. Nature, distribution and function of plant flavonoids. Prog Clin Biol Res 1986;213:15-24.

55. Javed H, Khan MM, Ahmad A, Vaibhav K, Ahmad ME, Khan A, et al. Rutin prevents cognitive impairments by ameliorating oxidative stress and neuroinflammation in rat model of sporadic dementia of Alzheimer type. Neuroscience 2012;210:340-52.

56. Nassiri-Asl M, Mortazavi SR, Samiee-Rad F, Zangivand AA, Safdari F, Saroukhani S, et al. The effects of rutin on the development of pentylenetetrazole kindling and memory retrieval in rats. Epilepsy Behav 2010;18:50-3.

57. Drew G, Schachtschabel DO, Falgan K, Grzanka A, Sujkowska R. The influence of rutin on the weight, metastasis and melanin content of B16 melanotic melanoma in C57BL/6 mice. Neoplasma 1998;45:266-71.

58. Wang XD. Carotenoids. In: Ross CA, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, editors. Modern Nutrition in Health and Disease. 11th ed. Philadelphia: Lippincott Williams & Wilkins; 2014. p. 427-39.

59. Rodriguez AD. A Guide to Carotenoid Analysis in Foods. Washington, DC, USA: ILSI Press; 2001. p. 1-64.

60. Costa A, Lindmark L, Arruda LH, Assumpção EC, Ota FS, Pereira Mde O, et al. Clinical, biometric and ultrasound assessment of the effects of daily use of a nutraceutical composed of lycopene, acerola extract, grape seed extract and biomarine complex in photoaged human skin. An Bras Dermatol 2012;87:52-61.

61. Wu WB, Chiang HS, Fang JY, Hung CF. Inhibitory effect of lycopene on PDGF-BB-induced signalling and migration in human dermal fibroblasts: A possible target for cancer. Biochem Soc Trans 2007;35:1377-8.

62. Beppu F, Niwano Y, Tsukui T, Hosokawa M, Miyashita K. Single and repeated oral dose toxicity study of fucoxanthin (FX), a marine carotenoid, in mice. J Toxicol Sci 2009;34:501-10.

63. Kumar SR, Hosokawa M, Miyashita K. Fucoxanthin: A marine carotenoid exerting anti-cancer effects by affecting multiple mechanisms. Mar Drugs 2013;11:5130-47.

64. Kim KN, Ahn G, Heo SJ, Kang SM, Kang MC, Yang HM, et al. Inhibition of tumor growth in vitro and in vivo by fucoxanthin against melanoma B16F10 cells. Environ Toxicol Pharmacol 2013;35:39-46.

65. Imbs TI, Ermakova SP, Fedoreyev SA, Anastyuk SD, Zvyagintseva TN. Isolation of fucoxanthin and highly unsaturated monogalactosylglycerol from brown alga fucus evanescens C agardh and in vitro investigation of their antimutator activity. Mar Biotechnol (NY) 2013;15:606-12.

66. Chung TW, Choi HJ, Lee JY, Jeong HS, Kim CH, Joo M, et al. Marine algal fucoxanthin inhibits the metastatic potential of cancer cells. Biochem Biophys Res Commun 2013;439:580-5.

67. Gerster H. Anticarcinogenic effect of common carotenoids. Int J Vitam Nutr Res 1993;63:93-121.

68. Kohlmeier L, Hastings SB. Epidemiologic evidence of a role of carotenoids in cardiovascular disease prevention. Am J Clin Nutr 1995;62:1370S-6S.

69. Ames BN, Shigenaka MK, Hagen TM. Oxidants, antioxidants, and the degenerative diseases of aging. Proc Natl Acad Sci U S A 1993;90:7915-22.

70. Palozza F, Serini S, Torsello A, Di Niculo F, Maggiano N, Ranelletti FO, et al. Mechanism of activation of caspase cascade during beta-carotene-induced apoptosis in human tumor cells. Nutr Cancer 2003;47:76-87.

71. Bialy TL, Rothe MJ, Grant-Kels JM. Dietary factors in the prevention and treatment of nonmelanoma skin cancer and melanoma. Dermatol Surg 2002;28:1143-52.

72. Millen AE, Tucker MA, Hargr E, Halpern A, Elder DE, Guerry D 4th, et al. Diet and melanoma in a case-control study. Cancer Epidemiol Biomarkers Prev 2004;13:1042-51.

73. Qiu S, Sun H, Zhang AH, Xu HY, Yan GL, Han Y, et al. Natural alkaloids: Basic aspects, biological roles, and future perspectives. Chin J Nat Med 2014;12:401-6.

74. Donoso JA, Himes RH. The action of two vinca alkaloids on B16 melanoma in vitro. Cancer Biochem Biophys 1984;7:133-45.
Kurangi and Jalalpure: Herbal phytoconstituents for melanoma treatment

77. Bang JS, Oh DH, Choi HM, Sur BJ, Lim SJ, Kim JY, et al. Anti-inflammatory and antiarthritic effects of piperine in human interleukin 1beta-stimulated fibroblast-like synoviocytes and in rat arthritis models. Arthritis Res Ther 2009;11:R49.

78. Wattanathorn J, Chompatornkiunlert P, Muchimapura S, Priprem A, Tankaermannthai O. Piperine, the potential functional food for mood and cognitive disorders. Food Chem Toxicol 2008;46:3106-10.

79. Bhardwaj RK, Glaser H, Becquemont L, Klotz U, Gupta SK, Fromm MF, et al. Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4. J Pharmacol Exp Ther 2002;302:645-50.

80. Peram MR, Jalalpure SS, Palkar MB, Diwan PV. Stability studies of pure and mixture form of curcuminoids by reverse phase-HPLC method under various experimental stress conditions. Food Sci Biotechnol 2017;26:591.

81. Fofaria NM, Kim SH, Srivastava SK. Piperine causes G1 phase cell cycle arrest and apoptosis in melanoma cells through checkpoint kinase-1 activation. PLoS One 2014;9:e94298.

82. Han X, Shen T, Lou H. Dietary polyphenols and their biological significance. Int J Mol Sci 2007;8:950-88.

83. Pandey RR, Rizvi SL. Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev 2009;2:270-8.

84. Thresiamma KC, Kuttan R. Inhibition of liver fibrosis by ellagic acid. Indian J Physiol Pharmacol 1996;40:363-6.

85. Losso JN, Bansode RR, Trappey A 2nd, Bawadi HA, Truax R. In vitro anti-proliferative activities of ellagic acid. J Nutr Biochem 2004;15:672-8.

86. Kim S, Liu Y, Gaber MW, Bumgardner JD, Haggard WO, Yang Y, et al. Development of chitosan-ellagic acid films as a local drug delivery system to induce apoptotic death of human melanoma cells. J Biomed Mater Res B Appl Biomater 2009;90:145-55.

87. Shimogaki H, Tanaka Y, Tamai H, Masuda M. In vitro and in vivo evaluation of ellagic acid on melanogenesis inhibition. Int J Cosmet Sci 2000;22:291-303.

88. Shen T, Xie CF, Wang XN, Luo HX. Stilbenoids. In: Ramawat KG, Merillon JM, editors. Natural Products. Berlin, Germany: Springer; 2013. p. 1901-49.

89. Gatouillat G, Balasse E, Joseph-Pietras D, Morjani H, Madoulet C. Resveratrol induces cell-cycle disruption and apoptosis in chemoresistant B16 melanoma. J Cell Biochem 2010;110:893-902.

90. Osmond GW, Augustine CK, Zipfel PA, Padussis J, Tyler DS. Enhancing melanoma treatment with resveratrol. J Surg Res 2012;172:109-15.

91. Asensi M, Medina I, Ortega A, Carretero J, Baño MC, Obrador E, et al. Inhibition of cancer growth by resveratrol is related to its low bioavailability. Free Radic Biol Med 2002;33:387-98.

92. Guan H, Singh NP, Singh UP, Nagarkatti PS, Nagarkatti M. Resveratrol prevents endothelial cells injury in high-dose interleukin-2 therapy against melanoma. PLoS One 2012;7:e35650.

93. McDanell R, McLean AE, Hanley AB, Heaney RK, Fenwick GR. Chemical and biological properties of indole glucosinolates (glucobrassicins): A review. Food Chem Toxicol 1988;26:59-70.

94. Fimognari C, Hrelia P. Sulforaphane as a promising molecule for fighting cancer. Mutat Res 2007;635:90-104.

95. Juge N, Mithen RF, Traka M. Molecular basis for chemoprevention by sulforaphane: A comprehensive review. Cell Mol Life Sci 2007;64:1105-27.

96. Arcidiacono P, Ragonese F, Stabile A, Pistilli A, Kuligina E, Rende M, et al. Antitumor activity and expression profiles of genes induced by sulforaphane in human melanoma cells. Eur J Nutr 2017. DOI 10.1007/s00394-017-1527-7.

97. Pradhan SJ, Mishra R, Sharma P, Kundu GC. Quercetin and sulforaphane in combination suppress the progression of melanoma through the down-regulation of matrix metalloproteinase-9. Exp Ther Med 2010;1:915-20.

98. Thejass P, Kuttan C. Modulation of cell-mediated immune response in B16F-10 melanoma-induced metastatic tumor-bearing C57BL/6 mice by sulforaphane. Immunopharmacol Immunotoxicol 2007;29:173-86.