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Next-Gen therapeutics for Skin Cancer: Nutraceuticals

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Abstract

Growing modernization and lifestyle changes with limited physical activity have impacted diet and health, leading to an increased cancer mortality rate worldwide. As a result, there is a greater need than before to develop safe and novel anticancer drugs. Current treatment options such as chemotherapy, radiotherapy and surgery, induce unintended side effects, compromising patient's quality of life and physical well-being. Therefore, there has been an increased global interest in the use of dietary supplements and traditional herbal medicines for treatment of cancer. Recently, nutraceuticals or 'natural' substances isolated from food have attracted considerable attention in the cancer field. Emerging research suggests that nutraceuticals may indeed prevent and protect against cancer. The intent of this article is to review some of the current spice-derived nutraceuticals in the treatment of melanoma and skin cancer.

Keywords

Curcumin; Ginger; Herbs

Introduction

The term 'nutraceuticals' was coined in 1989 by Stephen L. DeFelice, MD, an American medical doctor [1]. A nutraceutical is any food-derived supplement that has a medical benefit in preventing illness and promoting health [2]. Nutraceuticals often can be used interchangeably with terms such as dietary supplements, dietary ingredients or functional food [3]. Although, dietary supplements may not necessarily be derived from foods, nutraceuticals, on the other hand, are exclusively derived from foods. Thus, nutraceuticals are natural bioactive products that have promising therapeutic properties for treatment of a wide range of diseases [4–12].

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Emerging research suggests that diet and nutrition play an important role in maintaining good health [13–14]. Consuming nutrient dense foods and regular physical activity are of utmost necessity for maintaining a healthy, balanced life. Physical inactivity is now a major global epidemic and a serious risk factor for a plethora of diseases [15–16]. Unbalanced consumption of food and lack of physical activity are associated with increased risk of anxiety, stress, mood disorders, obesity, diabetes, blood pressure and even cancer [17–19].

Cancer is a major global threat. It is the world's second leading cause of mortality and morbidity. In 2016, the National Cancer Institute reported that an estimated 1,685,210 new cases of cancer will be diagnosed in the United States and 595,690 people will die from the disease [20]. The need to scale-up cancer treatment is urgent. With the growing body of research, the use of alternative or unconventional treatment medicine appears to be increasing [21–22]. It is reported that nearly 40% of the adults in the U.S. use alternative medicine and dietary supplements [23]. This widespread use of dietary supplements has brought attention to the importance of diet and nutrition in the pathogenesis of cancer.

Nutraceuticals: promising science for cancer

The transformation of a normal cell to a malignant cell is a multistep process wherein the normal cell undergoes a series of alterations to become malignant. As we know now, cancer is not a single disease, but rather a complex network of a group of diseases. There are more than 200 types of cancer, each with its unique signs, symptoms, and mechanisms [24]. The most prevalent forms of cancer in the US are breast, colorectal, prostate, pancreatic, kidney, liver, lung, and melanoma [20].

Skin cancer is by far the most common type of cancer [25]. Since skin is the largest organ in the body, and the most important barrier against heat, cold, light, and infection, it is prone to insults. In fact, the most skin-related injuries are a direct result of exposure to the UV radiations in the sunlight. Overexposure to the sunlight can cause DNA damage in skin cells, leading to uncontrolled growth, cell proliferation, and ultimately cancer [26–27]. Despite the considerable advances in the treatment options for cancer, undue side-effects associated with chemotherapy and radiotherapy still compromise the patient's quality of life and physical well-being. Furthermore, post cancer treatment complications such as nausea, vomiting, fatigue, pain, change in taste or smell and bowel movement lead to severe weight loss, muscle mass loss, weakness, dysregulated satiety and low energy [28–29]. Since diet and nutrition form an important component of good health, consuming the right kinds of nutrients before and after treatment can help improve a patient's quality of life and life expectancy [30–33]. Hence, there is an ever-growing emphasis for the use of nonconventional or alternative medicines to treat cancer.

Although the predisposition of cancer cannot be reduced to a single factor, studies have demonstrated a strong association between dietary choices, genetic background and cancer incidence rates [33–34]. Cancer rates are more prevalent in western countries, whereas cancer incidence rates are much lower in Asian countries [35]. Not surprisingly, the western diet is characterized by processed fast food, large portions of red meat, high-fat dairy products, and high-sugar drinks, while the Asian diet is comprised of low-fat, well-balanced healthy cuisine emphasizing whole-grains, relatively low meat, large portions of vegetables,

fruits, and plenty of spices. In addition, many different Asian countries practice natural plant-based herbal medicines for health management. Ayurveda, the traditional Indian medicine, [36] and the traditional Chinese herbal medicines [37] are the two systems of medicine. Although in some cases, there is no well documented scientific evidence, these remain as living traditions around the world. Not surprisingly, many of these plant-derived dietary agents, called “nutraceuticals”, have found a place in the global market [3].

Nutraceutical, a term formed by combing two words: “nutrition” and “pharmaceuticals” is defined as any natural substance derived from food or a part of a food itself that provides medical benefit [3]. During the past few years, a number of nutraceuticals have been identified from natural sources such as spices, herbs, botanical raw materials and extracts [38–39]. More than 182 spice-derived nutraceuticals have been well-documented [40–41]. Indeed, adding some “spice to your life” shows great potential for fighting cancer, skin-related diseases, infection, inflammation, obesity and many other diseases [41]. In this review, we attempt to summarize some of the promising nutraceuticals including turmeric, garlic, ginger, cloves, rosemary, saffron and capsaicin in the context of melanoma and skin cancer.

Spices as nutraceuticals

The Indian subcontinent is a huge repository of a wide variety of spices which have characteristic aroma, taste, texture, and color [42]. In fact, India is referred to as the “home of spices.” Spices can be used either whole, chopped, ground, roasted, sautéed, fried or as a topping on foods. Throughout the ancient period, spices have earned high value in the Indian culture, serving a variety of purposes, including coloring agent, food additives, flavoring agents and as preservatives. Moreover, early records indicate the use of herbs and spices as being medicinal [43–45].

Ayurveda, the oldest known system of medicine that was developed between 2500 and 500 BC, offers treatment methods to cure many illnesses and allergies, using plant-based herbal remedies [44–45]. The Sanskrit word Ayurveda literally means “science of life,” is derived from the root word “ayuh” which means life and “veda” meaning science or knowledge. In Ayurveda, nutrition and diet play import roles for healthy living. As per the Ayurvedic understanding of disease etiology, diseases arise because of an imbalance between three fundamental bio-elements or the *doshas* called Vata (airy element), Pitta (firey element) and Kapha (watery element) [44–46]. These three *doshas* form the heart of the Ayurvedic lifestyle which states that each one of us is made up of unique combinations of Vata, Pitta and Kapha. Therefore, a balance between these three forces that create a physical body is necessary to maintain a healthy equilibrium [44]. Moreover, Ayurveda also believes that plants and plant products can have a strong impact on physical and mental states of well-being [43]. In addition to plant-based diet, Ayurveda believes that spices in our diet can help bring balance to our *doshas.* Hence, Ayurveda preaches that plant-based products and spices should constitute the major portion of our diet [45–46]. Not surprisingly, in India, even to this day, a major section of the population depends on the traditional vegetarian diet wherein spices form the heart of Indian cooking.

Today, Indian spices are most sought-after globally. India is the world's largest producer, consumer and exporter of spices. It contributes 75% of global spice production. A total of 109 varieties of spices have been listed under the International Organization for Standardization (ISO) [46]. Ayurveda, the traditional system of medicine reveals that spices have an immense influence on quality of health. Furthermore, a growing body of research shows that spices have anti-inflammatory, anti-bacterial, anti-tumorigenic and anti-oxidative properties [47–48]. There exists a wide range of beneficial effects for treating skin disorders, allergies, digestion, constipation, metabolic disorders, reproductive problems and cancer.

Nutraceuticals for skin cancer patients

Skin cancer rates are rising steadily. It is estimated that if rates of melanoma, one of the deadliest forms of skin cancer, continue to increase, 112,000 new cases will be diagnosed in 2030 [49]. Melanoma is often treatable if diagnosed at an early stage; hence, there is a constant push to develop the latest treatment options. The annual cost of treating skin cancers in the U.S. is estimated at $8.1 billion of which nearly $4.8 billion is for nonmelanoma skin cancers and $3.3 billion is for melanoma [49]. With the growing skin cancer rates plus mounting health care costs, there is an increased desire to maintain a healthy lifestyle. Hence, to promote quality of life, scientists are focusing on the role of diet and nutrition in disease prevention.

In the Asian subcontinent, particularly in countries like India, Bangladesh, China, and Japan, there is a longstanding culture and tradition of using plant-derived spices as herbal remedies [40–42, 45–46]. Today, spices have become an integral part of diverse ethnicities around the world. The notion that spices can prevent diseases and illnesses has now gained much needed global recognition. Plenty of herbal plants grown in the tropics have a wide spectrum of medical uses. In addition, these products are less expensive, relatively safe and more readily available than the conventional drugs. Therefore, in this review we will focus on some of the more promising spice-derived nutraceuticals for skin cancer.

i) Turmeric—Turmeric, one of the oldest, most well-known and popular Ayurvedic spices, has been used for thousands of years [50–53]. Turmeric is derived from the root of Curcuma Longa, a member of the ginger family. It is native to Southeast Asia and widely used in countries like India, China, Malaysia, Indonesia, Bangladesh, and Pakistan. Turmeric is well recognized for its anti-inflammatory properties [51, 54–56]. Curcumin, one of the best studied compounds for cancer prevention, is the main active ingredient of turmeric [53]. On average, curcumin accounts for about 3.14% of powdered turmeric [53]. Currently, curcumin is under extensive research for its anti-oxidant, anti-inflammatory and anti-carcinogenic properties [51–52, 54–55]. Curcumin is an effective reactive oxygen species (ROS) scavenger and has been shown to attenuate mediators of inflammatory responses [55, 56–58]. Chronic inflammation and oxidative stress has been linked to cancer and several other diseases [59]. Studies have shown that turmeric and curcumin show effective anti-oxidant properties *in-vivo* and *in-vitro* [54]. The anti-inflammatory property of curcumin is thought to result from its ability to inhibit the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway [58, 60], an inducible transcription factor that regulates genes such as cyclooxygenase-2 (COX-2), nuclear factor of kappa light polypeptide gene enhancer in B-

cells inhibitor-alpha (IkB-α), tumor necrosis factor-alpha (TNF-α), cyclin D1, c-myc, B-cell lymphoma-2 (Bcl-2), inducible nitric oxide synthase (iNOS) and interleukins. The anti-cancer potential of turmeric stems from its ability to directly interact with and suppress a wide variety of pro-carcinogenic signaling molecules and transcription factors such as NF-kB [61]. In human melanoma patients, NF-kB expression is shown to be upregulated [60]. Inhibiting NF-kB appears to be a promising option for anticancer treatments. Additionally, phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/protein kinase B (AKT)/ mitogen-activated protein kinases (MAPK) and extracellular signal–regulated kinases (ERK) pathway also play a major role in skin carcinogenesis [62]. Curcumin has the ability to modulate the effects of TNF-α and MAPK pathway [61–62]. In a study by Kuttan R et al., turmeric and curcumin were found to produce remarkable symptomatic relief in patients with external cancerous lesions [63]. In a more recent study, it was demonstrated that topical application of curcumin-based cream was as effective as oral curcumin at suppressing tumor growth in a mouse skin cancer model *in vivo* [64]. In the same study, the anti-carcinogenic effect of curcumin on skin cancer was associated with inhibition of AKT/mTOR and ERK signaling [64].

Pharmacologically, curcumin is shown to be well-tolerated and relatively safe to use in patients. The clinical trials conducted thus far have reported relatively no toxicity [52]. Phase I clinical trial conducted by Cheng et al. showed that oral administration of 8 g/day of curcumin for 3 months is non-toxic to patients with high-risk or pre-malignant lesions [65]. In phase II trial of curcumin in patients with advanced pancreatic cancer, it was shown to downregulate the NF-κB, cyclooxygenase-2 (COX-2), and phosphorylated signal transducer and activator of transcription 3 in peripheral blood mononuclear cells from patients [66]. In another phase II pilot study, a combination of docetaxel, prednisone and curcumin was well-tolerated and accepted in patients with castration-resistant prostate cancer [67]. Therefore, turmeric and curcumin continue to be explored as a potential therapeutic agent for treatment of skin cancer.

ii) Ginger—*Zingiber officinale* (ginger) is a well-known herb, consumed as a spice in traditional Asian and European cooking, and used as a medicine in India and China since ancient times [68–69]. It is also widely used as a flavoring agent in food and drink, and as a fragrance in soaps and cosmetics. Ginger is one of the examples of ‘superfoods’ that has been used for centuries for its remarkable health benefits. Several biological active compounds have been identified and synthesized from ginger. Chemical analysis of ginger shows that it contains more than 400 biological compounds [69–70]. 6-gingerol, one of the active compounds synthesized from ginger, is being investigated for its anti-inflammatory, anti-bacterial, anti-angiogenic and anti-carcinogenic properties [70–72]. Ginger is a ‘miracle drug’ for cancer patients. Not only is it safe and effective to use, but ginger’s well recognized use is in its ability to offset side effects of chemotherapy such as vomiting and nausea [73]. It has been shown to be effective against colorectal cancer, pancreatic cancer, ovarian, breast, gastric, and skin cancers [74–78]. Ginger and its bioactive molecules are known to inhibit growth and angiogenesis in human ovarian cancer cells [79]. It has been shown to exert its anti-inflammatory and anti-angiogenic effects through inhibition of NF-κB, Interleukin-8 (IL-8) expression and vascular endothelial growth factor (VEGF)

secretion, the most important inducer of angiogenesis [79]. 6-gingerol exhibited cytotoxicity by growth inhibition via generation of ROS in human epidermoid carcinoma cells [80]. Topical application of ginger extract on rats inhibited UV-induced skin damage and photoageing through inhibition of COX-2 mRNA and protein, as well as NF-kB translocation from cytosol to nucleus [81–82]. Pre-treatment of ginger was shown to reduce UVB-induced expression of cytokines, ROS, activation of caspases (3, 8, 9), and Fas expression in vitro and in vivo [82]. In JB6 skin carcinogenesis model (murine skin epidermal cells), gingerol was shown to block epidermal growth factor (EGF)-induced cell transformation and inhibit EGF-induced activator protein-1 (AP-1) DNA binding activity [83]. Katiyar et al., showed for the first time that topical application of ginger (1,2, or 4 mg/animal) was effective in inhibiting chemically-induced carcinogenesis in mice [84]. Preapplication of ginger extract onto the skin of mice resulted in significant inhibition of 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-caused induction of epidermal ornithine decarboxylase (ODC), cyclooxygenase, and lipoxygenase activities [84], suggesting that extracts of ginger possesses anti-skin tumor-promoting effects.

Since numerous preclinical trials have shown that ginger and its active ingredients exert anti-carcinogenic properties [71–72, 74–84], ginger extracts are being tested on cancer patients as well [73]. In the 2017 pilot study, the anti-oxidant activity of ginger extract, as a daily supplement was examined in newly diagnosed cancer patients receiving adjuvant chemotherapy [85]. In these patients, ginger extract could increase antioxidant enzyme blood levels, including superoxide dismutase-1 (CuZn-SOD or SOD1) and catalase (CAT) activity, and levels of glutathione peroxidase (GPx) and glutathione/glutathione disulfide (GSH/GSSG) and decrease oxidative stress blood levels, including malondialdehyde (MDA) and nitrite/nitrate (NO_2^-/NO_3^-), as compared to the placebo [85]. These studies collectively suggest that ginger could be effectively used for the treatment of skin cancer.

iii) Garlic—Allium sativum (Garlic) is another commonly used flavoring agent and has been an herbal remedy for centuries [86]. Garlic belongs to the family of Liliaceae and Allium class of bulb-shaped plants which includes onions, scallions, and chives [87]. It is one of the best-studied compounds for its anti-inflammatory, anti-viral, anti-bacterial and anti-oxidant properties [88]. Garlic is rich in sulfur-containing compounds (allicin), and contains flavonoids, selenium, and arginine which are all beneficial to health [89]. Several studies have shown an inverse correlation between daily garlic intake and cancer risk [90–91]. Increased garlic intake is known to reduce the risk of stomach, esophageal, breast, pancreatic, and skin cancers [90–93]. Taylor et al. first reported the anti-metastatic effect of garlic sulfur (ajoene) compounds [94]. In the same study, it was shown that garlic at a dose of 100 ug/animal was effective to inhibit TNF-α, IL-6 production and serum cytokine levels, which is suggestive of a strong anti-carcinogenic and anti-inflammatory activity [94]. Oral and topical application of garlic has shown promising results against chemically induced skin pappilomagenesis in mice. In a recent study by Shan et al., diallyl disulfide (DADS), another major garlic derivative, dose-dependently attenuated skin tumor incidence and multiplicity in a multistage skin carcinogenesis model *in vivo* [95]. The anti-cancer mechanism of DADS was thought to be related to upregulation of anti-oxidant enzymes such as SOD, catalase, heme oxygenase (HO), GPx and the nuclear accumulation of nuclear

factor (erythroid-derived 2)-like 2 (Nrf2). Hence, DADS is a potential anti-cancer compound for skin cancer. In a similar study by Das et al., daily garlic consumption as diet delayed the onset of skin papilloma formation and reduced the number and size of skin papillomas in mice [93]. Garlic exerted its chemopreventive properties by modulating p53 and PI3K/AKT signaling pathway, down-regulating COX-2, as well as promoting ROS and apoptosis in skin papilloma cells [93].

Not surprisingly, many clinical studies have reported possible cancer-preventive effects of garlic and its derivatives [91]. Topical application of ajoene was shown to be effective against patients with either nodular or superficial base cell carcinoma (BCC) [96]. Ajoene-induced reduction in tumor size was seen in 17 out of 21 patients [96]. In a meta-analysis by Zhou et al., it was showed that consumption of large amounts of total *allium* vegetables could reduce risk of gastric cancer [97]. In addition to cancer, topical applications of garlic extract hold great promise in dermatology and skin-related disorders. A double-blinded randomized controlled trial conducted by Hajheydari et al., showed that garlic gel could be an effective adjunctive topical therapy for alopecia areata, a common skin disease causing hair loss [98]. Therefore, these results together indicate that garlic promotes an anti-cancer effect in skin and several other organs.

iv) Cloves—Syzygium aromaticum *L* (cloves), are sun-dried, unopened flower buds, commonly used as flavoring agent, spice and medicinal in Ayurveda. Cloves are known to possess active compounds with anti-microbial, anti-bacterial, anti-septic, anti-oxidant, and anti-carcinogenic properties [99–101]. Historically, in ancient India, cloves were used to treat respiratory problems, digestive problems and tooth-aches [102]. As a result, even to this day, cloves remain an active ingredient in toothpaste and mouthwash in India. Major different essential oils have been synthesized from cloves such as eugenol (principle component 82–90%), caryophyllene, alpha-humulene, alpha-terpinyl acetate, eugenyl, methyl eugenol, actyl eugenol, naphthalene, chavicol, heptanone, sesquiterpenes, methyl salicylate pinene, and vanillian. The major chemical constituents of clove include sesquiterpenes, volatile oil (eugenol), caryophyllene, tannins, and gum [102–103]. There are several reports that suggest the anti-cancer properties of cloves and its compounds [103]. Eugenol, has been shown to suppress lipid peroxidation [104–105]. In another study, bis-eugenola synthesized by the oxidation of eugeno, inhibited activation of NF-kB through the suppression of lipopolysaccharide (LPS)-stimulated IκB degradation [106]. In addition, bis-eugenola inhibited LPS-stimulated expression of cytokines. In a study in 1997, Oya et al. reported that cloves are strong scavengers of ROS and inhibited the formation of MDA [107]. Clove infusion (100 ul/mouse/day) inhibited cell proliferation and induced apoptosis in benzol[a]pyrene-induced lung carcinogenesis in mice [108]. The chemopreventive potential of cloves was thought to be through the upregulation of expression of pro-apoptotic proteins p53 and Bax, and downregulation of anti-apoptotic protein Bcl-2. In addition clove infusion downregulated the expression of growth-promoting proteins such as COX-2, c-myc, and H-ras [108]. In the same study, they showed that the incidence of hyperplasia, dysplasia and carcinoma were effectively reduced after treatment with clove infusion, suggesting that clove infusion has anti-proliferative and apoptogenic properties. Evidence also exists that clove extract can be used to treat skin cancer as well. Aqueous infusion of clove (100 μl/day/

animal) was found to reduce the incidence and multiplicity of mouse skin papilloma in a dose dependent manner, indicating a promising role of cloves in skin carcinogenesis [109]. These observations suggest cloves have a promising role in the restriction of carcinogenesis. While no studies have been conducted in cancer patients to evaluate the efficacy of cloves, studies performed both *in vitro* and *in vivo* suggest its effectiveness as an anti-cancer agent.

v) **Rosemary—***Rosmarinus Officinalis* L. (rosemary), an herbal plant and member of a mint family *Lamiaceae* is native to the Mediterranean region and has many uses. Leaves of rosemary are commonly used as spice, flavoring agents and as antioxidants. Rosemary extract is a rich source of polyphenols such as diterpenes carnosic acid (CA) and rosmarinic acid (RA) [110]. Polyphenols are powerful anti-oxidants. Hence, rosemary leaves are commercially used for their naturally high antioxidant activity [111–112]. Brewer et al., reported that rosemary extract, at 100 mcg/mL was able to scavenge 39% of the DPPH radicals [113]. At 500 mcg/mL, it was able to scavenge 55% and rosemary extract at 100 mcg/mL) inhibited liposome oxidation by 98% [113]. Not surprisingly, rosemary extracts and their polyphones are being explored for their potential anti-carcinogenic properties [114]. Since many compounds that possess anti-oxidative properties are also effective in inhibiting skin tumorigenesis [115–116], a growing body of research indicates that topical application of rosemary and/or rosemary extracts inhibit skin cancer. In a study in 1994, it was found that the application of rosemary to mouse skin had a strong inhibitory effect on TPA-induced increases in ornithine decarboxylase activity, inflammation, hyperplasia, and tumor promotion [117]. Analysis of rosemary extracts revealed that carnosol and ursolic acid account for over 90% of anti-oxidant properties of rosemary extracts, and were strong inhibitors of TPA-induced skin carcinogenesis [118]. Carnosol is a good ROS scavenger and has been shown to inhibit 5-lipoxygenase activity [119]. Huang et al., reported that carnosol treatment inhibited migration and invasion of B16/F10 mouse melanoma cells suppressing matrix metallopeptidase 9 (MMP-9) mRNA though down-regulation of NF-kB, c-jun, and several upstream regulators of MMP-9 such as AKT, p38, and JNK and ERK1/2 [120]. In another study, the oral administration of rosemary extract (500 mg/kg body wt/mouse) was found to be significantly protective against two-stage skin tumorigenesis in mice [121]. Study results indicated that rosemary extract prolonged the latency period of tumor occurrence, decreased the tumor incidence, tumor burden and tumor yield and also significantly reduced the level of lipid peroxidation. One of the mechanisms by which rosemary extract rendered protection against carcinogenesis is attributed to rosemary extract-induced elevation of GSH levels [121]. In a more recent study, it was demonstrated that rosemary extract was able to efficiently reduce proliferation of the human melanoma A375 cell line through both cytotoxic and cytostatic effects in a dose and time dependent manner [122]. More importantly, they showed that rosemary treatment of melanoma cells induced a significant reduction of levels of proteins crucial for cellular homeostasis maintenance, such as protein disulfide-isomerase A3 (PDIA3), neutral alpha-glucosidase AB (GANAB) and lamin A [122]. Thus suggesting that down-regulation of these proteins could hamper normal cellular functions and induce endoplasmic reticulum (ER) stress. In fact, pharmacological and therapeutic potential of rosemary extracts not only pertain to treatment of skin cancer, but also to, colon, rectal, prostate, gastric, and breast cancers [123]. Due to these diverse activities, rosemary extracts either alone or in combination with other essential

herbs are being tested for clinical efficacy and safety. In 2015 a randomized comparative trial by Panahi et al., compared clinical efficacy of rosemary oil and minoxidil, an antihypertensive vasodialator, for the treatment of androgenetic alopecia (AGA), commonly called male or female pattern baldness [124]. Their findings provided evidence with respect to efficacy of rosemary oil in the treatment of AGA. Rosemary oil along with other essential oils such as thyme, lavender, and atlas cedar have been used as aromatherapy to treat patients with alopecia areata, a common autoimmune skin disease [125]. Another pilot trial evaluated the combination of reduced iso-alpha-aids from hops, oleanolic acid and rosemary extract in patients with rheumatic disease [126]. Therefore, these studies indicate that rosemary, a perennial herb, has the potential to be a novel and a safe chemotherapeutic.

vi) Saffron—*Crocus sativus* L**,** commonly called saffron**,** is a spice derived from a flower saffron crocus, a plant native to Southwest Asia. Saffron is one of the world's most expensive spices. It is commonly used as a food coloring agent in traditional Indian, Chinese and Mediterranean diets. More importantly, it has been used as an herbal remedy for various ailments for centuries [127–128]. It holds a very prominent place in the systems of medicine. In Ayurveda, saffron has numerous applications [129]. It is used to cure chronic diseases such as asthma and arthritis, to treat colds and coughs, acne and several skin diseases [129–130]. Chemical analysis has revealed the presence of more than 150 bioactive compounds in saffron [130–131]. In addition, saffron is a rich source of carotenoids, mainly crocin and crocetin. Studies have demonstrated that dietary intake of carotenoids is associated with potent anti-tumor effects [132]. Their anti-carcinogenic properties stems from the ability to suppress the activation of inflammatory cytokines, PI3K/AKT activation, Wnt signaling activity and pro-oncogenic transcription factors such as AP-1 [132]. Given that, saffron consists of powerful caratenoid components, saffron provides a varied and accessible platform for drug discovery. Plentiful data points to the ability of saffron to be used as a chemotherapeutic. Saffron has been used to inhibit gastric, colorectal, hepatic, pancreatic, prostate, breast, cervical, ovarian, and skin cancers [133–135]. Aqueous saffron preparation has been reported to inhibit chemically-induced skin carcinogenesis in mice [136]. Oral infusion of saffron either before or after 7,12-Dimethylbenz[a]anthracene (DMBA) treatment in mice was found to increase the levels of anti-oxidants such as glutathione S-transferase (GST), catalase, superoxide dismutase (SOD) and glutathione peroxidase (GPx) and significantly suppressed the levels of ROS in DMBA-induced skin carcinoma in mice [136]. In addition, Saffron ingestion inhibited the formation of skin papillomas and simultaneously reduced the tumor size in mice, suggesting that anti-cancer activity may be due to the induction of cellular defense systems [136]. Crocetin, a carotenoid constituent derived from saffron, is thought to be an effective anti-tumor agent [128]. Numerous in vivo and in vitro studies reported that Crocetin's anti-cancer effects were through the inhibition of nucleic acid synthesis in tumor cells, enhancing anti-oxidative system, and hindering growth factor signaling pathways [137–138]. In skin cancer cells, it has also been shown that crocetin causes a reduction in synthesis of DNA, RNA, protein and inhibit activity of RNA polymerase II in transformed cells [128,138–141]. It is also shown to interfere with histone H1 structure and histone-DNA interaction. In addition, it has also been demonstrated that crocin significantly induces apoptosis through the activation of Bax-Bcl-2 ratio and induces caspase activation [139]. These various *in vitro* and *in vivo* studies

highlight the potential of crocin and crocetin in treatment of human malignancies. A few well-designed clinical trials have reported the safety and efficacy of saffron in treatment of several mood discords. Talaei et al., conducted a double-blind, placebo-controlled and randomized pilot clinical trial to investigate the efficacy of crocin in treatment of major depressive disorder [142]. Their results demonstrated that the crocin group had significantly improved scores on beck depression inventory (BDI), beck anxiety inventory (BAI), general health questionnaire (GHQ), the mood disorder questionnaire compared to placebo group [142]. Another placebo-controlled trial indicated the efficacy of saffron in the treatment of mild to moderate Alzheimer's disease [143]. These results suggest that saffron is both safe and efficacious in treatment of several diseases. Taken together, these studies indicate that saffron could be used as a powerful anti-tumor agent.

vii) Capsaicin—Capsaicin, the key compound responsible for the pungency of red chillies or chilli peppers, belongs to the plant family Capsicum. Capsaicin is produced as plant-secondary metabolites and is commonly consumed around the world. They are not only used as food additives and coloring agents, but they also have a widespread application in pharmaceuticals. In fact, topical application of capsaicin is an approved treatment for neuropathic pain [144]. Creams, lotions and patches containing capsaicin are now sold in many countries, including the U.S. often without the requirement of a prescription, for the management of neuropathic and musculoskeletal pain. Also, topical application of capsaicin has been used in cancer patients to manage neuropathic pain resulting from surgery [145–146]. In 1997, a phase III placebo-controlled study reported that topical application of capsaicin cream decreases postsurgical neuropathic pain [145]. Another similar randomized, double blind, placebo-controlled study indicated that topical application of capsaicin, either as repeated application of a low dose (0.075%) cream, or a single application of a high dose (8%) patch provides a degree of pain relief to patients with neuropathic pain [146]. Although, no serious toxic side-effects were seen, this study reported of local mild skin irritation in some patients. Recently, capsaicin has been investigated for its anti-cancer potential against human lung, gastric, prostate, and skin cancers [147–150]. Capsaicin is thought to be an effective free radical scavenger and is shown to induce apoptosis in cancer cells [149]. Administration of capsaicin showed a significant decrease in liver oxidative stress and a significant increase in catalase activity in rats [150]. In human small cell lung cancer cells, capsaicin exhibited pro-apoptotic activity via down-regulating transient receptor potential vanilloid (TRPV-1) receptor, a family of transient receptor potential cation channel that contributes to heat and inflammation [151]. In another study, capsaicin was shown to induce anti-migration and anti-invasion effects in cholangiocarcinoma cells through inhibition of NF-κB and p65 [152]. Yet another study showed the chemoprotective potential of capsaicin in prostate cancer [153]. They showed that capsaicin induced prostate cancer cell death in a time- and concentration-dependent manner through the generation of ROS. Although, studies pertaining to the use of capsaicin for skin cancer treatments have been controversial [154], medical application of capsaicin already exists for the treatment of skin conditions like burning, itching, stinging and redness of skin. Topical application of capsaicin has been used in the treatment of psoriasis [155–156]. These studies open the possibility of using capsaicin for the treatment of skin cancer as well.

Are these *in vitro* and *in vivo* studies predictive of human pathology?

Animal and cell model are being increasingly used in the study of carcinogenesis. Such models have revolutionized our ability to study various molecular pathways, mechanisms, and for assessment of drug efficacy, toxicity and metabolism. Therefore, successful bench-to-bedside transition of scientific findings into therapeutic drugs depends on various internal, external, and environmental factors including selection of appropriate experimental model. Although cells and animals could provide useful information, *in vitro* systems do not provide physiological makeup for human factors. In fact, there is a serious concern about the predictive power of cell and animal models. This is not surprising considering the fact that cells such as human fibroblasts do not reflect a system as complex as human skin. Although, these studies show great benefits in cell and animal models, a more in-depth understanding of clinical trials would further strengthen these observations.

Conclusion

Mounting evidence suggests that diet and nutrition play a promising role in the fight against cancer. Cancers are not an inevitable cause of aging, but rather, a disease that can be preventable, largely through lifestyle changes [33]. This review brings to light the importance of adding spice or spice-derived nutraceuticals in one's diet. Spices are known to have a plethora of health benefits. Many of the spices mentioned in this article have been regarded as an integral component of many different cultures around the world. They have been used for a variety of purposes, such as flavoring agents, coloring agents, and as preservatives. In addition, spices have been used as herbal therapies for centuries. Numerous studies have documented the anti-inflammatory, anti-proliferation, anti-microbial, and anti-oxidant properties of spices (Table 1). Since oxidative stress, inflammatory stress and immune system stress have been associated with the genesis, progression, proliferation and metastasis of cancer [56], spices could be used to prevent and/or treat cancer [36–37, 40–41]. With a growing body of evidence, spices have begun to receive more attention as potential anti-cancer agents. This review summarizes the recent studies on some spice-derived nutraceuticals for treatment of skin cancer.

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Table 1.

List of Spices

Origin	Active Ingredient	Mechanism of Action
Turmeric	Curcumin	Anti-inflammation: Inhibits NF-kB pathway. Anti-oxidant: Reduces ROS and increases ROS scavenging enzymes. Anti-carcinogenic: Suppresses TNF-α, PI3K/ AKT, mTOR, MAPK and ERK signaling.
Ginger	Gingerols, shogaols	Antiemetic: Inhibits serotonin receptors. Anti-angiogenic: Inhibits NF-kB pathway, IL-8 and VEGF-induced cell proliferation. Anti-inflammatory: Reduces expression of cytokines. Anti-carcinogenic: Inhibits growth and tumor proliferation, reduces ROS, blocks NF-kB activation and increases anti-oxidant enzymes.
Garlic	Allicin	Anti-oxidative: Prevents intracellular GSH depletion, inhibits NK-kB activation, and removes peroxides and upregulates antioxidant enzymes. Immunomodulatory effects: Inhibits both pro- and anti- inflammatory cytokines and regulates COX-2. Anti-carcinogenic: Delays onset of tumorigenesis by modulating p53 and PI3K/AKT signaling pathway, promotes apoptosis, inhibits TNF-α, IL-6 production and serum cytokine levels.
Cloves	Eugenol	Anti-oxidant: Reduces oxygen radicals, superoxide, hydrogen peroxide, and increases GSH. Anti-microbial: Denatures microbial proteins, reacts with cell membrane phospholipid and inhibits the growth of microbes. Anti-carcinogenic: Inhibits proliferation, inhibits activation of COX-2, c-myc, H-ras, upregulates pro-apoptotic proteins and down-regulates anti-apoptotic proteins.
Rosemary	Rosemarinic acid, carnosic acid	Anti-oxidative: Causes free radical scavenging reduces lipid peroxidation and inhibits DPPH radicals. Anti-inflammatory: Inhibits secretion of pro-inflammatory cytokines and TNF-α. Anti-carcinogenic: Inhibits NF-kB activation, suppresses MMP-9, c-jun, ERK, AKT and p38 signaling and metabolic activation of pro-carcinogens and induces ROS detoxification pathway such as GST.
Saffron	Crocin, crocetin	Anti-depressant: Increases serotonin levels in the brain and inhibits serotonin reuptake in synapses. Anti-oxidant: Increases the levels of GST, catalase, SOD and GPx and suppresses ROS formation. Anti-carcinogenic: Inhibits growth of tumor cells via inhibiting nucleic acid and protein synthesis in malignant cells, induces apoptosis via activation of Bax-Bcl-2, and suppresses PI3K, AKT, Wnt, PKC activity.

Origin	Active Ingredient	Mechanism of Action
Capsaicin	Capsaicin	Analgesic: Activates TRPV1 resulting in sensory neuronal depolarization and depletion of substance P. Anti-carcinogenic: Inhibits ROS, induces apoptosis, and attenuates tumor cell migration and invasion through inhibition of NF-kB activity.