Pharmacological Research 119 (2017) 327–346

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Diet phytochemicals and cutaneous carcinoma chemoprevention: A review

Siliang Wang[a,1], Peiliang Shen[a,1], Jinrong Zhou[c], Yin Lu[a,b,*]

[a] Jiangsu Key Laboratory for Pharmacology and Safety Evaluation of Chinese Materia Medica, School of Pharmacy, Nanjing University of Chinese Medicine, Nanjing 210023, PR China
[b] Jiangsu Collaborative Innovation Center of Traditional Chinese Medicine (TCM) Prevention and Treatment of Tumor, Nanjing University of Chinese Medicine, Nanjing 210023, PR China
[c] Nutrition/Metabolism Laboratory, Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA

ARTICLE INFO

Article history:
Received 6 October 2016
Received in revised form 25 January 2017
Accepted 4 February 2017
Available online 24 February 2017

Keywords:
Cutaneous carcinoma chemoprevention
Diet phytochemicals
Redox homeostasis
Epigenetic modulators
Cutaneous inflammation
Cancer neovascularization
Metastasis

ABSTRACT

Cutaneous carcinoma, which has occupied a peculiar place among worldwide populations, is commonly responsible for the considerably increasing morbidity and mortality rates. Currently available medical procedures fail to completely avoid cutaneous carcinoma development or to prevent mortality. Cancer chemoprevention, as an alternative strategy, is being considered to reduce the incidence and burden of cancers through chemical agents. Derived from dietary foods, phytochemicals have become safe and reliable compounds for the chemoprevention of cutaneous carcinoma by relieving multiple pathological processes, including oxidative damage, epigenetic alteration, chronic inflammation, angiogenesis, etc. In this review, we presented comprehensive knowledges, main molecular mechanisms for the initiation and development of cutaneous carcinoma as well as effects of various diet phytochemicals on chemoprevention.

Contents

Abbreviations: Akt, protein kinase B; AMPK, adenosine 5′-monophosphate (AMP)-activated protein kinase; Ang, angiopoietin; AP-1, activator protein 1; ARE, antioxidant-responsive element; ATF-2, activating transcription factor 2; BCC, basal cell carcinoma; Bcl-2, B-cell lymphoma 2; Bcl-Xl, B-cell lymphoma-extra large; Bmi-1, B lymphoma Mo-MLV insertion region 1 homolog; CCL2, chemokine (C-C motif) ligand 2; CDK, cyclin-dependent kinases; c-FLIP, cellular Fas-associated death domain-like interleulin-1 β converting enzyme inhibitory protein; CF-TP, polyphenol fraction of Crataegus pinnatifida; COX-2, cyclooxygenase-2; CPDs, cyclobutane pyrimidine dimers; CREB, cAMP response element-binding protein; CXCL8, chemokine (C-X-C motif) ligand 8; DATS, diallyl trisulfide; DMBA, 7,12-dimethylbenz[a]anthracene; DNMTs, DNA methyltransferases; EC, endothelial cells; ECM, extracellular matrix; EGCG, epigallocatechin gallate; EP, prostaglandin E2 receptor; ERK, extracellular signal–regulated kinases; Ezh2, enhancer of zeste homolog 2; FAK, focal adhesion kinase; FGF, fibroblast growth factors; GCL, glutamate cysteine ligase; GM-CSF, granulocyte-macrophage colony-stimulating factor; GPx, glutathione peroxidase; GSH, glutathione; GST, glutathione S-transferases; HATs, histone acetyltransferase; HDACs, histone deacetylase; HDMs, histone demethylase; HH, hedgehog; HIF-1α, hypoxia-inducible factor-1 alpha; HMTs, histone methyltransferases; HO-1, heme oxygenase 1; HPVs, human papilloma viruses; IBD, inflammatory bowel disease; IKK, IκB kinase; IL, interleukin; iNOS, inducible nitric oxide synthases; JNK, c-Jun N-terminal kinases; Keap1, kelch-like-ECH-associated protein 1; LPSs, lipopolysaccharides; MAPK, mitogen-activated protein kinases; MC1R, melanocortin 1 receptor; MDA, malonaldehyde; MITF, microphthalmia-associated transcription factor; MMP, matrix metalloproteinase; m-TOR, mammalian target of rapamycin; TXA2, thromboxane A2; MVD, microvascular density; NF-κB, nuclear factor kappa-light-chain enhancer of activated B cells; NMSC, non-melanocytic cutaneous carcinoma; NO, •nitric oxide; NQO, NAD(P)H:quinoneoxidoreductase; Nrf2, nuclear factor (erythroid-derived 2)-like 2; PCNA, proliferating cell nuclear antigen; PDGF, platelet-derived growth factor; PGE2, prostaglandin E2; PGI2, prostaglandin I2; PI3K, phosphatidylinositol-3-kinases; PKC, protein kinase C; PLGF, Placental growth factor; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; SCC, squamous cell carcinoma; STAT3, signal transducer and activator of transcription 3; TIMP-1, tissue inhibitor of metalloproteinases 1; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor alpha; TPA, 12-O-Tetradecanoylphorbol-13-acetate; TSP-1, thrombospondin 1; UVR, ultraviolet radiation; VEGF, vascular endothelial growth factor; XIAP, X-linked inhibitor of apoptosis protein; γ-GCS, γ-glucocorticoids; TSG, tumor suppressor genes.

* Corresponding author at: Jiangsu Key Laboratory for Pharmacology and Safety Evaluation of Chinese Materia Medica, School of Pharmacy, Nanjing University of Chinese Medicine, Nanjing 210023, PR China.
E-mail address: profyinlu@163.com (Y. Lu).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.phrs.2017.02.021
1043-6618/

1. Introduction

Till now, cutaneous carcinoma is the most common human malignancy (especially in the white population) due to steadily rising life expectancy, increasing urbanization and subsequent lifestyle changes, with millions of new cases detected worldwide each year [1–4]. Although the incidence rate for all cancer sites combined is decreasing, the cutaneous carcinoma incidence rate has continued to increase, which is a significant public health problem that exacts a substantial financial and social burden [5].

Cutaneous carcinoma is generally classified as malignant melanoma and non-melanocytic cutaneous carcinoma (NMSC). The latter includes squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) as the main subtypes that are named according to the originating cells and clinical behaviors [6]. NMSC are much more frequent than melanoma, but they have a better prognosis. Both, basal and squamous cell carcinomas, originate from epidermal keratinocytes and both appear mainly in cutaneous areas exposed to sunlight [7]. BCC accounts for the majority of NMSC cases (about 80%–85%) and has a low rate of metastasis to other organs, while 15%–20% of NMSC are SCC with a higher tendency to metastasize and higher mortality than BCC [8,9]. Melanoma, which is derived from epidermal melanocytes, represents only 4% of cutaneous carcinoma cases, yet accounts for 80% of all cutaneous carcinoma-related deaths [6]. Limited progress has been made in the treatment of cutaneous carcinoma over the past 4 decades, through the use of immunotherapy, chemotherapy, radiotherapy, targeted therapy and combinations, which have yielded reduced response rates and low median survival, associated with significant toxic profiles and treatment resistance. Thus, the burden of cutaneous carcinoma remains chronically high [10,11,262].

Development of cutaneous carcinoma is a multistep process that involves initiation, promotion and progression (Graphical abstract). Mutation and abnormalities of key cellular regulators (e.g. *RAS, p53, EGFR* and *p16INK4A*), as early events in tumorigenesis, are caused by various carcinogens (eg. UV) directly or through inducing epigenetic alterations and intracellular oxidative stress [12]. Due to subsequent failure of these genes, an accumulating cellular malignant phenotype may appear by activating transcriptional factors such as NF-κB, β-catenin, STAT3, HIF-1α and AP-1, as well as their downstream proteins. As a result, cutaneous carcinoma can be discerned owing to the inflammatory microenvironment together with uncontrollable cell growth and differentiation [13]. Besides, continuous inflammatory conditions and disturbed transcriptional factors activation may further lead to tumor-related angiogenesis and metastasis that are significant pathological indicators of lethal cutaneous carcinoma. Chemopreventive strategies have been reported to control such hyperactive signaling cascades and pathological alterations which may delay and reverse these multistep process of cutaneous carcinoma and lower the burden [14–16].

Over two-thirds of human cancers may be prevented by appropriately modifying the lifestyle, especially by changing the dietary habit [17]. Being responsible for color and other organoleptic properties, diet phytochemicals are chemical compounds naturally constituted in plant-based food [17–19]. Resveratrol, epigallocatechin gallate (EGCG) and curcumin have been reported to directly regulate a variety of molecular signal transduction pathways, which participate in cancer initiation, promotion or progression. Eventually, they can reduce the incidence and death rates of human neoplasms, such as cutaneous carcinoma [20–22].

In this review, we introduced the basic knowledge of cutaneous carcinoma, and highlighted the causative factors and their influences on the intracellular signaling cascades involved in cancer development. In addition, we shed light on some phytochemicals capable of targeting the signaling pathways which make them applicable to cutaneous carcinoma chemoprevention and control of its progression. On this basis, we also expounded the potential correlation between the these compounds and clinical outcome.

2. Risk factors for cutaneous carcinoma

High awareness of the risk factors for cutaneous carcinoma is crucial for prevention. Although why the incidence and death rates of cutaneous carcinoma have ascended so dramatically in recent years remains unclear, they may be attributed to multiple endogenous and exogenous factors. The most common risk factors are discussed as follows.

2.1. UVR

The vast majority of cutaneous carcinoma are caused by UV exposure from the sun and/or indoor tanning devices [23–26,264].