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Review

Regulation of cell signaling pathways by dietary agents for cancer prevention and treatment

Manoj K. Pandey[a,*], Subash C. Gupta[b], Ali Nabavizadeh[a], Bharat B. Aggarwal[c]

[a] Department of Biomedical Sciences, Cooper Medical School of Rowan University, Camden, NJ, USA
[b] Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi, India
[c] Inflammation Research Center, San Diego, CA, USA

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ABSTRACT

Although it is widely accepted that better food habits do play important role in cancer prevention and treatment, how dietary agents mediate their effects remains poorly understood. More than thousand different polyphenols have been identified from dietary plants. In this review, we discuss the underlying mechanism by which dietary agents can modulate a variety of cell-signaling pathways linked to cancer, including transcription factors, nuclear factor κB (NF-κB), signal transducer and activator of transcription 3 (STAT3), activator protein-1 (AP-1), β-catenin/Wnt, peroxisome proliferator activator receptor- gamma (PPAR-γ), Sonic Hedgehog, and nuclear factor erythroid 2 (Nrf2); growth factors receptors (EGFR, VEGFR, IGF1-R); protein Kinases (Ras/Raf, mTOR, PI3K, Bcr-abl and AMPK); and pro-inflammatory mediators (TNF-α, interleukins, COX-2, 5-LOX). In addition, modulation of proteasome and epigenetic changes by the dietary agents also play a major role in their ability to control cancer. Both *in vitro* and animal based studies support the role of dietary agents in cancer. The efficacy of dietary agents by clinical trials has also been reported. Importantly, natural agents are already in clinical trials against different kinds of cancer. Overall both *in vitro* and *in vivo* studies performed with dietary agents strongly support their role in cancer prevention. Thus, the famous quote "Let food be thy medicine and medicine be thy food" made by Hippocrates 25 centuries ago still holds good.

1. Introduction

A cancer develops by a complex interaction of activated signaling pathways, awry mutations, and uncontrolled cell division [1,2]. Despite the announcement of National Cancer Act in 1971 by the then United States President, Richard Nixon, cancer is still the number one cause of death. With advancement in modern molecular tools, we now know that cancer is caused by dysregulation of multiple genes [3]. Yet, most of the drugs are mono-targeted [4]. Thus, it is highly unlikely that targeting of a gene, protein, or signaling pathway will be helpful for the prevention and treatment of cancer [5]. Therefore, alternative approaches are required.

According to the recent report from World Cancer Research Foundation, approximately 10% of all cancers are caused by either genetic or somatic mutations, while remaining 90% has been attributed to epigenetic changes such as environment and lifestyle [6]. The common risk factors for cancer are alcohol, tobacco, food carcinogens, pollutants, obesity, and stress [7–11]. The process that links risk factor and cancer is known as inflammation [12,13]. All risk factors associated with cancers are proven to be pro-inflammatory [14–16]. Importantly, better diet and physical activities can prevent approximately one third of all cancers [17–19]. Supporting this notion, ample evidences from published literature suggest that ingredients from dietary foods possess potential for the cancer prevention and treatment [17,20,21]. Furthermore, studies have demonstrated that dietary agents possess anti-inflammatory properties [22]. The dietary agents are structurally diverse (Fig. 1) and modulate unique targets that are linked with angiogenesis, invasion, metastasis, proliferation, and survival (Fig. 2). A number of studies demonstrated that natural agents target receptors, kinases, transcription factors, and inflammatory mediators such as chemokines (Table 1).

In this review, we discuss how cancer related signaling components including pro-inflammatory components, growth stimulators, receptors, transcription factors, and kinases contribute to cancer pathogenesis. How dietary agents target these signaling molecules and thereby help in the cancer prevention and treatment is also discussed.

2. Cell signaling pathways linked to cancer

As described in the above section, cancer is caused by dysregulation

* Corresponding author at: Dept. of Biomedical Sciences, Cooper Medical School of Rowan University, 401 S Broadway, Camden, NJ 08103, USA.
E-mail address: pandey@rowan.edu (M.K. Pandey).

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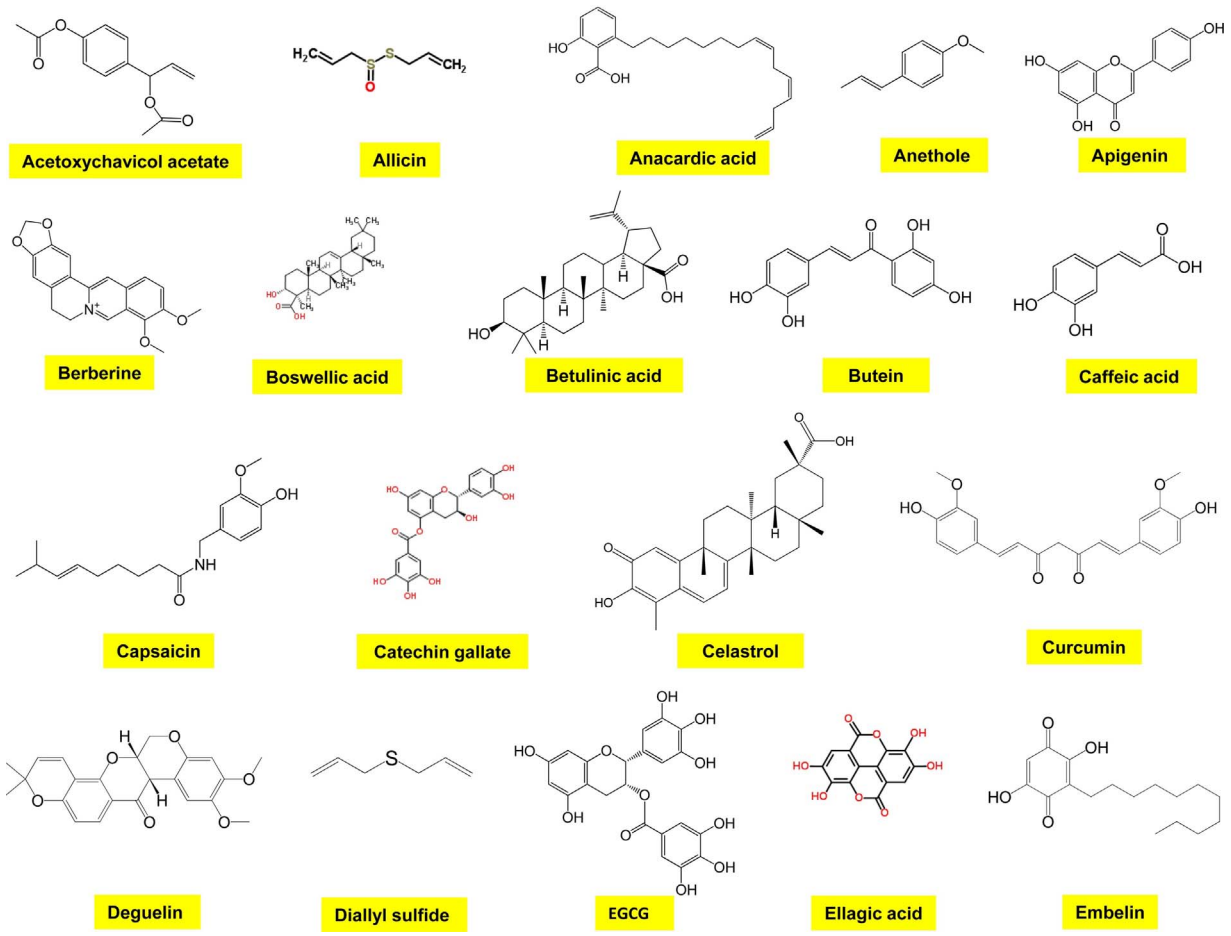

Fig. 1. Chemical structure of common dietary agents.

of multiple signaling molecules (Fig. 3). In this section, we discuss some of the crucial components of cancer cell signaling which are integral in tumorigenesis.

3. Transcription factors

The transcription factors are class of proteins that bind to unique sequences on DNA, and control the rate of transcription, thus help in regulation of gene expressions [23,24]. These transcription factors work alone or in association with other proteins [24]. The majority of cancer cells show the aberrant levels of transcription factors [24]. Because down regulation in transcription factors is associated with suppression in tumor growth, these factors have been well regarded as potential target for therapeutic inventions [25]. The most widely studied transcription factors include NF-κB, STAT3 and AP-1[26–29]. Reports from our group and by others have demonstrated a cross-talk among these transcription factors [30–32].

3.1. Nuclear factor-kappa b (NF-κB)

The nuclear factor-kappa B (NF-κB) is a pro-inflammatory transcription related component which was first discovered by Sen and Baltimore in 1984 [33]. To date, this factor regulates more than 500 genes. These genes are essential in angiogenesis, cell existence, inflammation, invasion, metastasis, and cell propagation [30,34,35]. The abnormal level of NF-κB is illustrated in various cancer biopsies and cancer cell lines [31,35,36].

Mainly five proteins constitute NF-κB: Rel A, Rel B, c-Rel, NF-κB1, and NF-κB2 [31,37]. A hetero trimer of NF-κB1, Rel A, and IκB subunits, sequesters inactively in cytoplasm. The IKK complex (IKKβ, IKKα, and NEMO) phosphorylates IκB proteins [38–40], which leads to its ubiquitination and proteasomal degradation, releasing p65/p50 complexes and nuclear translocation of complex. The p65 subunit binds to unique consensus sequence of a promoter region of genes and controls transcription [38]. It has been reported that most carcinogens, tumor promoters, free radicals, growth factors, and inflammatory agents activate an IKK complex.

In non-canonical (or alternative) NF-κB activation pathway, inactive complexes of NF-κB2 p100/RelB impound in the cytoplasm [41,42]. A variety of signaling mediated by LTβR, CD40, and BR3, activates NIK kinase, which initiates cascade of events including activation of IKKα complex followed by NF-κB2 p100 phosphorylation, ubiquitination and proteasomal processing to NF-κB2 p52 [41,43]. After processing NF-κB p52/RelB complex translocate to the nucleus and regulates variety of genes [41–43], such as anti-apoptotic genes, COX-2, matrix metalloproteinase-9 (MMP-9), adhesion related genes, chemokines etc. [30,44,45]. Indeed, several studies using animal models have demonstrated that NF-κB is essential in tumorigenesis [46]. Additionally, over expression of c-Rel is also reported in number of cancers such as breast, non-small lung carcinoma, and head and neck cancer [47,48]. Furthermore, high expression of a complex of Bcl-3 and another subunit of NF-κB (p50) is reported in nasopharyngeal carcinoma [49]. Moreover, overexpression of NF-κB has been associated with lymphatic invasion, peritoneal metastasis and size of the tumor in gastric cancer [46,50].

3.2. Signal transducer and activator of transcription (STAT) family

So far, seven members in STAT family are characterized [51]. Of seven members, STAT3 is the best-studied transcription factor [52,53]. The characterized feature of STAT family proteins is presence of the Src

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