Pharmacological Research 130 (2018) 273–291

Contents lists available at ScienceDirect

Pharmacological Research

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

Review

Targeting oncogenic transcription factors by polyphenols: A novel approach for cancer therapy

Chitra Rajagopal[a], Manendra Babu Lankadasari[a], Jesil Mathew Aranjani[b], K.B. Harikumar[a,*]

[a] Cancer Research Program, Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram 695014, Kerala, India
[b] Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal 576104, Karnataka, India

ARTICLE INFO

Article history:
Received 31 July 2017
Received in revised form
30 November 2017
Accepted 31 December 2017
Available online 4 January 2018

Chemical compounds studied in this article:
4- Shogaol (PubChem CID: 9794897)
6- Shogaol (PubChem CID: 5281794)
Apigenin (PubChem CID: 5280443)
Berberine (PubChem CID: 2353)
Bergamottin (PubChem CID: 5471349)
Caffeic acid (PubChem CID: 689043)Capsaicin (PubChem CID: 1548943)
Cardamonin (PubChem CID: 641785)
Casticin(PubChem CID: 5315263)
Chrysin (PubChem CID: 5281607)
Cryptotanshinone (PubChem CID: 160254)
Cucurbitacin (PubChem CID: 5281319)
Curcumin (PubChem CID: 969516)
EGCG (PubChem CID: 65064)
Ellagic acid (PubChem CID: 5281855)
Escin (PubChem CID: 16211024)
Fistein (PubChem CID: 5281614)
Gambogic acid (PubChem CID: 16072310)
Gingerol (PubChem CID: 442793)
Gossypin (PubChem CID: 5281621)
Honokiol (PubChem CID: 72303)
Luteolin (PubChem CID: 5280445)

ABSTRACT

Inflammation is one of the major causative factor of cancer and chronic inflammation is involved in all the major steps of cancer initiation, progression metastasis and drug resistance. The molecular mechanism of inflammation driven cancer is the complex interplay between oncogenic and tumor suppressive transcription factors which include FOXM1, NF-kB, STAT3, Wnt/β- Catenin, HIF-1α, NRF2, androgen and estrogen receptors. Several products derived from natural sources modulate the expression and activity of multiple transcription factors in various tumor models as evident from studies conducted in cell lines, pre-clinical models and clinical samples. Further combination of these natural products along with currently approved cancer therapies added an additional advantage and they considered as promising targets for prevention and treatment of inflammation and cancer. In this review we discuss the application of multi-targeting natural products by analyzing the literature and future directions for their plausible applications in drug discovery.

Abbreviations: AIF, apoptosis-inducing factor; Akt/PKA, protein kinase A; AR, androgen receptors; Bax, Bcl-2-associated X protein; Bcl2, B-cell lymphoma2; BIG3, brefeldin A-inhibited guanine nucleotide-exchange protein3; CCL2, chemokine ligand 2; Cdc25B, cell division cycle 25B; Cdk 2, cyclin-dependent kinase 2; Cdk4, cyclin-dependent kinase 4; c-FLIP, cellular FLICE- inhibitory protein; COX2, cyclooxygenase 2; CXCR2, C-X-C chemokine receptor type 2; DNMT1, DNA methyltransferase 1; EMT, epithelial to mesenchymal transition; ERK1, extracellular signal-regulated kinase-1; ERα, estrogen receptor alpha; FAK, focal adhesion kinase; FGF, fibroblast growth factors; FOXM1, forkhead box protein M1; Foxo3a, forkhead box O3; HIF-1α, hypoxia inducing factor-1α; hTERT, telomerase reverse transcriptase; IAP, the inhibitors of apoptosis protein; ICAM-1, intercellular adhesion molecule 1; IGF-1R, insulin-like growth factor 1; IKK, inhibitory kappa B kinase; iNOS, inducible nitric oxide synthase; IκBα, inhibitory kappa B alpha; JAK, janus kinase; JNK, c-Jun *N*-terminal kinase; LRP4, LDL receptor related protein; Mcl-1, myeloid leukemia cell differentiation protein; MDM2, mouse double minute 2 homolog; MMP, matrix metalloproteinase; mToR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; PAIS3, protein inhibitor of activated STAT protein 3; PARP, poly (ADP-ribose) polymerase; PCNA, proliferative cell nuclear antigen; PGE2, prostaglandin E2; PHB, prohibitin; PI3K, phosphoinositide 3-kinase; PSA, prostate-specific antigen; ROS, Reactive oxygen species; SHP1, src homology region 2 domain-containing phosphatase-1; SOCS3, suppressor of cytokine signaling 3; STAT, signal transducer and activator of transcription; TGFβ, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; uPA, urokinase-type plasminogen activator; VEGF, vascular endothelial growth factor; XIAP, X-linked inhibitor of apoptosis protein.

* Corresponding author.
E-mail address: harikumar@rgcb.res.in (K.B. Harikumar).

https://doi.org/10.1016/j.phrs.2017.12.034
1043-6618/

Mangiferin (PubChem CID: 5281647)
Piperlongumine (PubChem CID: 637858)
Pterostilbene (PubChem CID: 5281727)
Quercetin (PubChem CID: 5280343)
Resveratrol (PubChem CID: 445154)
Rutin (PubChem CID: 5280805)
Sesamin (PubChem CID: 72307)
Ursolic acid (PubChem CID: 64945)
Wogonin (PubChem CID: 5281703)
Xanthohumol (PubChem CID: 639665)

Keywords:
Polyphenols
Cancer
Inflammation
Metastasis
Natural compounds
Transcription factors

Contents

1. Introduction

Cancer is a multifactorial disease caused by dysregulation of numerous gene products and alteration of multiple cell signaling pathways. The key reasons for more than 90% of cancer are attributed to somatic mutations and environmental factors. Another major factor is epigenetic changes and research in recent years clearly demonstrated that DNA methylation and other type of histone modifications can lead to alterations in chromatin condensation status, thereby regulating the expression of specific genes. Any kind of perturbation in the expression of these genes can lead to cellular transformation eventually leading to cancer [1]. Several epidemiological, pre-clinical and clinical studies over the last several decades established the relationship between the process of inflammation and cancer. The acute inflammatory response has therapeutic advantages however chronic inflammation is associated with a myriad of diseases [2].

2. Natural products

Natural products can be defined as structurally diverse functional entities with multiple biological functions derived from natural sources such as plants [3]. Many of the currently using chemotherapeutics are derived from natural sources [4]. Polyphenols are a class of natural products present in various plant products like vegetables, fruits, seeds, legumes etc. Apart from yielding colour, aroma and taste to plants, they can also act as the major component of plant immune system [5–8]. It comprises of three main subclasses namely flavonoids, phenolic acids, and stilbenoids which include hydroxybenzoic acids, hydroxycinnamic acids, anthocyanins, proanthocyanidins, flavonols, flavones, flavanols, flavanones, isoflavones, stilbenes, lignansetc [5]. Its history of evolution as major class of phytochemicals in the field of therapeutics started from leather industry. Before 20th century, polyphenols were named as vegetable tannins used in the conversion of animal skin to leather. Later, its co-evolution along with molecular chemistry leads to its establishment as an important category of biomolecules in the field of therapeutics. Structural elucidation of polyphenols shows them as the polymers of phenol groups, poly-hydroxylated phytochemicals. Mode of extraction varies according to its physicochemical properties. Different extraction methods include solvent extraction, microwave assisted extraction, ultrasound assisted extractions etc which is followed by its colorimetric quantification [3,9]. Polyphenols are dominated for their antioxidant property but the recent research showed their ability to bind to certain proteins directly leading to physiological changes. Their antioxidant properties make them usable against different diseases like cancer, diabetes, cardiovascular diseases etc. [10]. They directly interacts with key enzymes, receptors, transcription factors and even with protein aggregates which changes different biochemical reactions and signaling pathways. These molecular level control mechanisms give their potency as promising agents against different diseases including cancer [3,9]. The Table 1 describes the various details of polyphenols discussed in the review which include their sources, scientifically documented major biological functions and structure.