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Research update

Enhancement of anticancer potential of polyphenols by covalent modifications

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ABSTRACT

As evidenced by a growing number of respective clinical trials, a promising and increasingly valued approach to cancer prevention is chemoprevention which is based on using synthetic, semisynthetic, or natural compounds with the aim of preventing, delaying, arresting, or reversing carcinogenesis. Research carried out in the last two decades indicates that natural polyphenols isolated from plants (as well as their derivatives and synthetic analogs) exhibit pleiotropic actions toward cancer cells and therefore they could be used in both cancer prevention and therapy. This review discusses selected covalent modifications of polyphenols as a means for increasing their anticancer potential in relation to the parent compounds. The modifications include hydroxylation, methylation, acylation, and galloylation, among others. They were demonstrated to enhance cytotoxic, pro-oxidant, antiproliferative, proapoptotic, proautophagic, and antimigratory activities of phenolics toward various cancer cell lines *in vitro*. Importantly, some derivatives proved to suppress tumor growth and metastasis in animal models more strongly than the parent compounds. Some of the above-mentioned covalent modifications were also shown to increase absorption and tissue distribution of tested phenolic compounds *in vivo*. Anticancer clinical trials with polyphenol derivatives therefore seem warranted.

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1. Introduction

Nowadays, cancer is one of the most frequent diseases occurring in the modern world. Despite the huge progress in cancer research and improvements in the very dynamic field of drug formulations, it still remains a major worldwide health problem. Global statistics show that about 14.1 million new cancer cases and 8.2 million deaths occurred in 2012 worldwide [1]. Results of epidemiologic studies imply the existence of a correlation between cancer incidence and a predominant diet in a given area [2–4]. Plant polyphenols are one of the most widespread groups of non-essential nutrients classified as phytochemicals. They are characterized by a high structural diversity which, in turn, results in a very wide range of biological activities, including anticancer activities [5,6]. The diversity of polyphenol structures results not only from a large variety of carbon backbone chains within this group of compounds but also from various modifications (e.g., hydroxylation, methylation, acylation, and glycosylation) of primary and secondary substituents [7,8]. Through modulating some metabolic and signal transduction pathways, phenolic compounds can act as, among others, antioxidative [9,10], antiproliferative [11,12], proapoptotic [13,14], antiangiogenic [15,16], and anti-inflammatory agents [17,18]. Furthermore, those compounds modulate activities of some enzymes and other functional proteins [19].

Phenolics can therefore influence the process of carcinogenesis through numerous mechanisms, which renders them suitable for use in various anticancer therapies. However, the most important obstacles hindering the success of therapy based on those compounds are their poor systemic bioavailability, low membrane permeability, physiological instability, oxidative degradation, and metabolic transformations [20,21]. Studies on enhancement of polyphenol bioavailability are ongoing to overcome difficulties in reaching their therapeutic concentrations in target tissues. Many of those studies are aimed at improving formulations of phenolics

Abbreviations: CDF, curcumin difluorinated; DGB1, digalloyl dimer B1; DGB2, digalloyl dimer B2; DIG, digalloylresveratrol; DMC, dimethoxycurcumin; DMF, dimethoxyflavone; dNTP, deoxynucleoside triphosphate; ECG, epicatechin-3-gallate; EGCG, epigallocatechin-3-gallate; GA, gallic acid; HBC, hydrazinobenzoylcurcumin; HHRAs, higher hydroxylated resveratrol analogs; HHS, hexahydroxystilbene; HPSB, hydroxypterostilbene; IHCH, 2E,6E-2-(1H-indol-3-yl) methylene-6-(4-hydroxy-3-methoxybenzylidene) cyclohexanone; MF, methoxyflavone; PMF, pentamethoxyflavone; RR, ribonucleotide reductase; THS, tetrahydroxystilbene; TMF, trimethoxyflavone; UPS, ubiquitin–proteasome system.

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with the use of the latest achievements in the field (e.g., micronization, phytosomes, cyclodextrins, dendrimers, implants, nanodisks, and nanofibers) or at searching for and synthesis of polyphenol derivatives and structural analogs exhibiting better pharmacological as well as pharmacokinetic properties [22,23]. Here, we present several types of covalent modifications of phenolic compounds (such as hydroxylation, methylation, acylation, and galloylation, among others) and discuss the results of a number of *in vitro* and *in vivo* studies on the influence of those modifications on anticancer potential of phenolics (Fig. 1).

2. Hydroxylation

Murias and co-workers synthesized five hydroxylated analogs of 3,4′,5-trihydroxy-*trans*-stilbene (resveratrol) (**1**) and studied their structure–activity relationships in terms of pro-/antioxidant properties and cytotoxicity toward human promyelocytic leukemia HL-60 cells [24]. Three of those analogs (3,3′,4′,5-tetrahydroxystilbene (**2**); 3,4,4′,5-tetrahydroxystilbene (**3**); and 3,3′,4,4′,5,5′-hexa hydroxystilbene (**4**)) were demonstrated to exert a more than 6600-fold higher antiradical activity than the parent compound. Moreover, hydroxystilbenes with ortho–hydroxyl groups exhibited higher cytotoxicity toward HL-60 cells (more than 3-fold) than resveratrol, indicating an increased anticancer activity. The observed enhanced cytotoxicity of ortho-hydroxystilbenes was related to the presence of ortho-semiquinones formed during metabolism or auto-oxidation [24]. Further, proapoptotic potentials of resveratrol and its analog **4** were compared in HL-60 cells [25]. After 72 h incubation, **4** caused 50% inhibition of cell viability (IC_{50}) at almost half the concentration of resveratrol (with IC_{50} values of 6.25 μM for **4** and 12 μM for resveratrol) and exhibited a synergistic effect (IC_{50} = 2 μM) when applied simultaneously with ascorbic acid. The acid might had prevented **4** oxidation, thus increasing its activity, whereas it itself did not act as a cytotoxic agent against HL-60. Similarly to resveratrol, **4** triggered apoptosis in those cells. However, it is worth noting that within the chosen concentration range the number of apoptotic cells was markedly higher in the case of **4** than in that of resveratrol (e.g., 100% and only 19%, respectively, at 25 μM). In addition, **4** arrested HL-60 in the S phase of the cell cycle, while depleting the cells in the G2-M phase, and triggered apoptosis by down-regulation of nuclear factor κB (NF-κB) and effective suppression of its activation by tumor necrosis factor α (TNF-α). The proapoptotic potential of **4** is also supported by the observation that, similarly to resveratrol, this analog destabilized the balance of intracellular deoxynucleoside triphosphates (dNTPs) through inhibition of ribonucleotide reductase (RR) activity. RR catalyzes the reduction of nucleoside triphosphates (NTPs) to dNTPs (necessary substrates for *de novo* DNA synthesis) and is highly upregulated in rapidly proliferating tumor cells [26].

Antitumor effects of M8 on melanoma were evaluated by Paulitschke and co-workers who determined that **4** inhibited the growth of M24met melanoma cells cultured *in vitro* and M24met cells isolated from xenografts after *in vivo* propagation [27]. After 48 h incubation, **4** showed the same IC_{50} values (approximately 25 μM) for M24met cells of both origins (i.e., cultured *in vitro* or isolated from xenografts). On the contrary, resveratrol was not able to inhibit the growth of those cells by 50% even at a four times higher concentration (100 μM). In addition, **4** proved to be a stronger antiproliferative agent than resveratrol against a melanoma cell line of lung metastasis (1205Lu), primary melanoma of cutaneous metastasis (MCM1, MCM19), primary melanoma of lymph node metastasis (MLNM1), and a gastric cancer cell line (MKN28). The analog caused cell cycle arrest through dose- and time-dependent upregulation of p21 (cyclin-dependent kinase inhibitor 1A, a transcriptional target of p53) and downregulation of CDK-2. Moreover, **4** stimulated the expression of p53 protein and induction of the proapoptotic proteins Bak and cleaved caspase-3. The number of apoptotic cells as well as DNA damage (detected by the comet assay) were higher in the case of M8 than

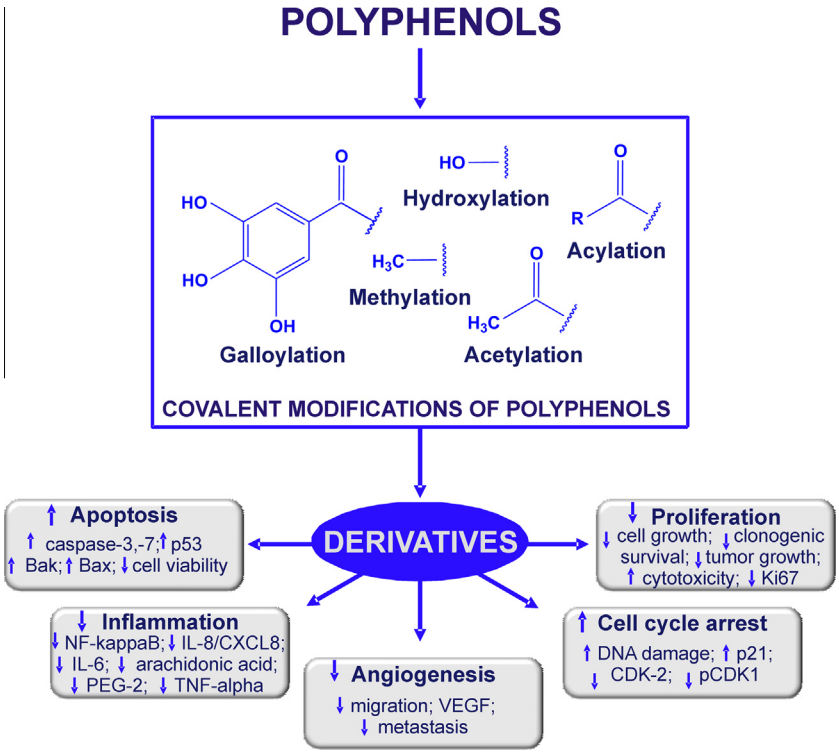

Fig. 1. A schematic summary of the influence of covalent modifications on anticancer potential of phenolics.

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