

Targeting proteasome by phenolic compounds in cancers

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Abstract—Nowadays, chemoprevention is considered as a promising approach for preventing premalignancy before transformation into invasive cancer. The development of drug is one of the biggest obstacles for prevention of cancer. The 26S proteasome is a proteolytic enzyme complex responsible for intracellular protein degradation especially in playing an important role for tumor growth. Phenolic compounds have multiple intracellular targets, one of which is the proteasome complex. Little attention has been devoted to studying the roles of natural antioxidants in the ubiquitin-proteasome pathway. The natural antioxidant polyphenolic compounds, methyl gallate, gallic acid, ellagic acid, and tannic acid from daily food, are known to inhibit certain carcinogen-induced cancers and effect on proteasome. In this review, the properties of polyphenolic compounds may provide cancer chemoprevention.

Index Terms--methyl gallate; gallic acid; ellagic acid; 26S proteasome inhibitor; tannic acid

THE PROTEASOME

Ubiquitin, a 76 amino acid, 8.6 kDa protein, is a small, conserved protein that is present in all known eukaryotic cells. Cellular organelles called proteasomes select polyubiquitin-tagged proteins for destruction [1]. The eukaryotic 26S proteasome, a proteolytic cellular apparatus, consists of two subunits: the 20S core particle and the 19S regulatory particle (19S cap, PA700) [2-3]. The structures of 26S proteasome is shown in Figure 1. The 20S core particle (20S CP), a cylindrical structure composed of 4-stacked rings, is a multicatalytic protease. The 2 outer rings (called α rings), in complex with the 19S regulatory particles, form a narrow channel through which only denatured proteins can pass. The catalytic chamber is formed by the 2 inner rings (called β rings), each of which contains 3 well-characterized peptidase activities, chymotrypsin-like, trypsin-like, and caspase-like hydrolytic active sites [4].

Two proteasome inhibitors, bortezomib and NPI-0052, have recently been reported in clinical trials. Bortezomib (Velcade, PS341) was the first of proteasome inhibitor to be used clinically [5]; however, the NPI-0052 was found to be more effective apoptosis inducer in lymphocytes from

chronic lymphocytic leukemia than bortezomib [6]. Natural active components from vegetables, tea, and fruit may used as oral 26S proteasomal inhibitor to prevent malignancy. The structures of methyl gallate, gallic acid, ellagic acid, and tannic acid are shown in Figure 2.

GALLIC ACID

Gallic acid (GA) is a type of phenolic acid. Its molecular formula is known as $C_7H_6O_5$ and molecular weight is 170.12. Almost all plants can be found gallic acid, but their content of gallic acid is not often rich. The plants known for their high content of gallic acid include gallnuts, grapes, tea, hops, and oak bark. It is also found both free and as a part of tannins.

The IC₅₀ of gallic acid in inhibiting purified 20S proteasome activity is 7.1 mM [7]. Although gallic acid had slightly inhibition on proteasome activities, gallic acid may upregulate p27(Kip1) level via disruption of p27(Kip1)/Skp2 association. Thus, p27(Kip1) is degraded by proteasome, leading to G2/M phase arrest of MCF-7 cell [8]. Gallic acid as one of the major constituents of grape seed extract showed strong in vitro anticancer efficacy against human prostate cancer cells [9]. Oral gallic acid feeding inhibits prostate cancer growth and progression to advanced-stage adenocarcinoma in TRAMP mice via a strong suppression of cell cycle progression and cell proliferation and an increase in apoptosis [10]. All these studies together indicate gallic acid has function other than inhibiting proteasome to cause cancer cells death [11].

METHYL GALLATE

Methyl gallate, a methyl ester of gallic acid, is a phenolic compound found in *Terminalia myriocarpa* [12] and *Geranium niveum* [13]. It is also found in food as wine, Winged Sumac fruits [14], and Thai mango (*Mangifera indica* L. cv. 'Fahlun') seeds [15]. Its molecular formula is $C_8H_8O_5$, and molecular weight is 184.15. Methyl gallate is an extremely potent compound with remarkable biological activities including antimicrobial, anti-inflammatory, and antiplatelet activities—with a tendency to act as an inhibitor of cell adhesion, cancer metastasis, skin papillomas, and carcinomas.

Methyl gallate exhibits potent antitumor activities by inhibiting tumor infiltration of CD₄⁺CD₂₅⁺ regulatory T cells [16]. Methyl gallate is effective in preventing DNA damage and oxidative stress in Madin-Darby canine kidney (MDCK) cells [17]. Methyl gallate has protective effects of on H₂O₂-induced apoptosis in PC12 cells [18]. An ester bond-containing molecule has the potential to inhibit the proteasomal chymotrypsin-like activity in vivo and in vitro

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[7]. Methyl gallate is a weak proteasome inhibitor, because it contains only one ester bond to be insufficient for potent proteasome inhibition.

Recently, it isn't any paper related to cancer treatment by methyl gallate yet. Meanwhile, wine containing methyl gallate is one of choice to against and prevent cancer.

ELLAGIC ACID

Ellagic acid is a polyphenolic antioxidant found in numerous fruits and vegetables such as blackberries, cranberries, pecans, pomegranates, raspberries, strawberries, walnuts, grapes, etc. [19]. Its molecular formula is $C_{14}H_6O_8$, and molecular weight is 302.197.

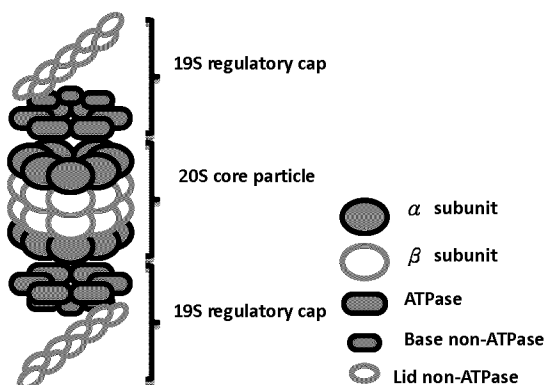


Figure 1. The structure of 26S proteasome [2]. 20S core particle is a multicatalytic protease. 19S regulatory particles, form a narrow channel through which only denatured proteins can pass.

In pre-clinical studies, ellagic acid have anticarcinogenic effects against liver [20], esophageal [21], prostate [22], colorectal cancer [23] cell lines. Ellagic acid can inhibit the proliferation, malignant potential, and chemoresistance of ovarian carcinoma cells [24]. Ellagic acid and quercetin interact synergistically with resveratrol in the induction of apoptosis via activated the caspase-3 pathway and cause transient cell cycle arrest in human leukemia cells [25]. Ellagic acid was found to induce apoptosis, which was blocked by pan-caspase inhibitor, Z-VAD-FMK; ellagic acid activated the caspase-3 pathway in human leukemia HL-60 cells [26]. Ellagic acid induced p53/p21 expression, G1 arrest, and

apoptosis in human bladder cancer T24 cells [27].

Quercetin combined with ellagic acid at 1:1 ratios did not inhibit purified 26S proteasomes activity [28].

Ellagic acid appears to inhibit chemical-induced esophageal carcinogenesis in rat [29]. However, human studies have yet to be conducted.

Although ellagic acid is not a strong proteasome inhibitor, ellagic acid might prevent from cancer via other pathways.

TANNIC ACID

Tannic acid (TA) is a specific commercial form of tannin and is a polyphenol that has shown anticancer activity. Tannic acid is a yellow powder with the molecular formula $C_{76}H_{52}O_{46}$, and its molecular weight is 1701.18. Tannic acid, the hydrolysable tannins, is widely found in food plants and widely used in various industrial food additives [30]. Tannins are plant-derived polyphenolic compounds and comprised of apentagalloylglucose core esterified at all functional hydroxyl groups with gallic acid molecules [31]. Tannic acid potently and specifically inhibits the chymotrypsin-like activity of purified 20S proteasome (IC₅₀ = 0.06 microg/ml), 26S proteasome of Jurkat T-cell extracts, and 26S proteasome of living Jurkat cells [32]. The previous study showed that the inhibitory effects of TA on the growth of malignant human cholangiocytes xenografts in vivo, and the potential use of proteasomal inhibitors for biliary tract malignancies [33]. The antiproliferative activity of lingonberry was caused predominantly by procyanidins --- tannin-rich fraction [34]. Combination of quercetin and tannic acid can inhibit 26S proteasome, affect on S5a and 20S expression, and accumulate ubiquitin resulted in apoptosis [28].

The plant foods are important in a cancer preventative diet. Understanding the structure-activity relationships of methyl gallate, gallic acid, ellagic acid, and tannic acid target the 26S proteasome is for the development of novel anticancer drugs. Natural products tannic acid can serve as a suitable chemopreventive agent and antioxidant for controlling cancer via ubiquitin-preteasome pathway.

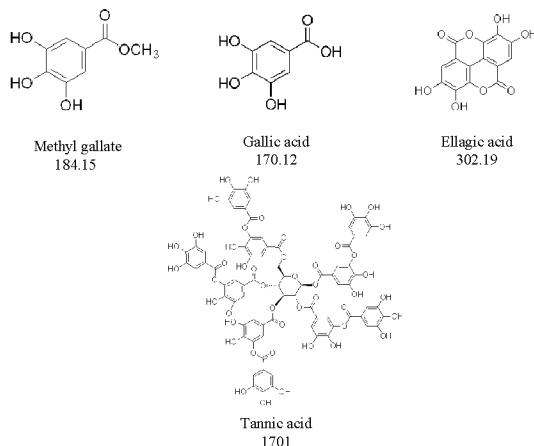


Figure 2. The structure and molecular weight of phenolic compounds



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BIOGRAPHIES

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