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Review

Oxidative breakage of cellular DNA by plant polyphenols: A putative mechanism for anticancer properties

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Abstract

Plant polyphenols are important components of human diet and a number of them are considered to possess chemopreventive and therapeutic properties against cancer. They are recognized as naturally occurring antioxidants but also act as prooxidants catalyzing DNA degradation in the presence of transition metal ions such as copper. We have shown that several of these compounds are able to bind both DNA and Cu(II) forming a ternary complex. A redox reaction of the polyphenols and Cu(II) in the ternary complex may occur leading to the reduction of Cu(II) to Cu(I), whose reoxidation generates a variety of reactive oxygen species (ROS). We have further confirmed that the polyphenol–Cu(II) system is indeed capable of causing DNA degradation in cells such as lymphocytes. We have also shown that polyphenols alone (in the absence of added copper) are also capable of causing DNA breakage in cells. Neocuproine (a Cu(I) sequestering agent) inhibits such DNA degradation. It also inhibits the oxidative stress generated in lymphocytes indicating that the cellular DNA breakage involves the generation of Cu(I) and formation of ROS. It is well established that tissue, cellular and serum copper levels are considerably elevated in various malignancies. Therefore, cancer cells may be more subject to electron transfer between copper ions and polyphenols to generate ROS. Thus, our results are in support of our hypothesis that anticancer mechanism of plant polyphenols involves mobilization of endogenous copper possibly chromatin bound copper and the consequent prooxidant action.

Keywords: Plant polyphenols; Endogenous copper; Prooxidant; Anticancer; Apoptosis; Reactive oxygen species (ROS)

Contents

1. Introduction

Plant-derived polyphenolic compounds that include flavonoids, tannins, curcuminoids, gallocatechins, stilbenes such as resveratrol, anthocyanidins such as delphinidin possess a wide range of pharmacological properties the mechanisms of which have been the subject of considerable interest (Fig. 1). They are recognized as naturally occurring antioxidants and have been implicated as antiviral and antitumor compounds [1,2]. In recent years, a number of reports have appeared which have shown that gallocatechins found in green tea and which include tannic acid, gallic acid, epigallocatechin, epicatechin-3-gallate and epigallocatechin-3-gallate (EGCG) induce apoptosis in various cancer cell lines [3,4]. Similarly curcumin [5] from the spice

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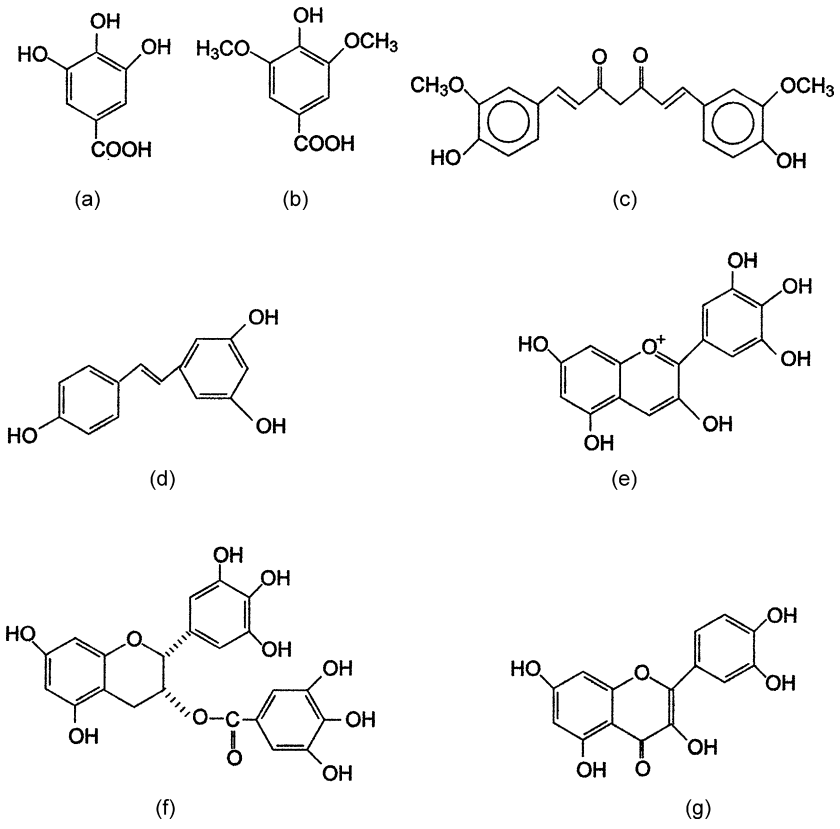

Fig. 1. Structures of (a) gallic acid, (b) syringic acid, (c) curcumin, (d) resveratrol, (e) delphinidin, (f) epigallocatechin-3-gallate, and (g) quercetin.

turmeric and resveratrol [6] which is found in grapes and red wine have also been shown to be inducers of apoptosis in cancer cells. The consumption of green tea is considered to reduce the risk of various cancers such as that of bladder, prostate, esophagus and stomach [4]. Of particular interest is the observation that EGCG was found to induce internucleosomal DNA fragmentation in cancer cell lines such as human epidermoid carcinoma cells, human carcinoma keratinocytes, human prostate carcinoma cells, mouse lymphoma cells but not in normal human epidermal keratinocytes [4]. Similarly gallic acid showed cytotoxicity for a number of tumor cell lines but primary cultured rat hepatocytes and macrophages were found to be refractory to the cytotoxic effect [3]. Resveratrol also was shown to induce apoptotic cell death in HL60 human leukemia cell lines but not in normal peripheral blood lymphocytes [6]. The hallmark of apoptosis is internucleosomal DNA fragmentation, which distinguishes it from necrosis. Other changes such as shrinkage of cells, membrane blebbing and the dissociation of the nucleus into chromatoid bodies also occur. It is to be noted that most clinically used anticancer drugs can activate late events of apoptosis (DNA degradation and morphological changes) and there are differences in essential signalling pathways between pharmacological cell death and physiological induction of programmed cell death [7]. Based on our own observations and those of others we propose a mechanism of DNA fragmentation in cancer cells by plant polyphenolics that involves mobilization of intracellular copper. Studies on chemopreventive and therapeutic plant-derived phytonutrients assume significance in view of the fact that such compounds exhibit negligible or low toxicity even at relatively high concentrations. Further they may also act as lead compounds for the synthesis and development of novel anticancer drugs.

2. Oxidative DNA cleavage by plant polyphenols *in vitro* in the presence of copper ions

Studies in our laboratory have shown that a number of plant polyphenols such as flavonoids [8], tannic acid and its structural constituent gallic acid [9], curcumin [10], gallocatechins [11] and resveratrol [12] cause oxidative strand breakage in DNA either alone or in the presence of transition metal ions such as copper. Recent studies by Liu and co-workers [13] demonstrated that resveratrol as well as its certain synthetic analogs namely 3,4,4′-trihydroxy-*trans*-stilbene, 3,4-dihydroxy-*trans*-stilbene, 3,4,5-trihydroxy-*trans*-stilbene, which are generally effective antioxidants, can switch to prooxidants in the presence of Cu(II) to induce DNA damage. Copper is an important metal ion present in chromatin and is closely associated with DNA bases particularly guanine [14,15]. It is also one of the most redox active of the various metal ions present in cells. We have also shown that the flavonoid quercetin [16] and curcumin [10] are capable of binding to DNA and copper. Evidence deduced in our laboratory has shown that polyphenols such as the flavonoid quercetin and the stilbene resveratrol can not only bind copper ions but also catalyze their redox cycling [12]. In the case of quercetin a mechanism was proposed which involved the formation of a ternary complex of DNA–quercetin–Cu(II) [17,16]. A redox reaction of the compound and Cu(II) in the ternary com-