Mechanism of Gallic Acid Anticancer Activity Through Copper-Mediated Cell Death

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Contents

Abstract

Plant-based polyphenolic compounds are present in various dietary sources and considered to possess antioxidant activity. Gallic acid (GA) is one particularly important polyphenol. Studies have reported that GA is cytotoxic to cancer cells while normal cells remain unaffected by such action. We suggested a mechanism that suggests the preferential killing of GA against cancer cell. Using Comet assay (single cell gel electrophoresis) and Fox assay (ferrous oxidation xylenol), it has been shown

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that GA behaves as prooxidant and causes DNA damage in human lymphocytes. Moreover, such DNA damage is stopped in the presence of copper chelator in cell validating the role of copper in the prooxidant DNA breakage by GA. Also, human breast cancer cell line (MDA-MB-231) growth is interrupted by GA resulting killing of cell in prooxidant manner. It is an established fact; copper levels are well elevated in different types of cancers. Consequently, cancer cells are subjected to transfer of electron between GA to produce ROS. Thus, we explain the cytotoxicity of GA towards malignant cells is because of elevated copper levels. In addition, our studies identify that nuclear copper can be responsible as a completely new target for cytotoxic behavior of GA as well as other polyphenolic compounds, which have strong potential against cancer as therapeutic agent.

Keywords

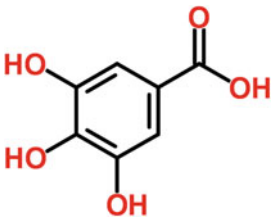
Gallic acid · Endogenous copper · Prooxidant DNA breakage · Cancer cells

Introduction

Cancer is a serious health problem around the globe. In recent years, the idea of preventing cancer has been attributed to the consumption of diet-based substances. It is believed that more than 70% of human cancers can be delayed or prevented by following proper lifestyle and eating habits. Epidemiological evidence suggests that increased utilization of fruits, vegetables, and beverages may curb the harmful risk of cancer induction (Adlercreutz et al. 1995; Park and Surh 2004; Barnes et al. 1994). This has been associated with human diet found to be rich in various biologically potent polyphenolic compounds (Surh 2003). Gallic acid (3, 4, 5-trihydroxybenzoic acid) is one such naturally available phenolic acid present in food stuff such as gall-nuts, green tea, apple, grapes and acts as potent antioxidant. The known pharmacological properties of GA include antitumor, antifungal, antibacterial, and antiviral activities. The anticancer effects of GA have been well demonstrated against cancer models, both in vitro and in vivo (Liang et al. 2012; Ji et al. 2009). GA has also been reported to induce apoptosis in human HSC-2 glioma cells, HL-60 cervical cancer cells, and human DU-145 promyelocytic leukemia cells while sparing normal cells (Alyssa et al. 2013; Madlener et al. 2007; Agarwal et al. 2006). The mechanism by which polyphenolic compounds prevent proliferation of cells and show apoptosis in malignant cells has always been a remarkably interesting field of research. Many mechanisms have been suggested. A clear and definitive mechanism to explain the anticancer properties of plant polyphenols is yet to be found.

Previous studies have shown that polyphenols belonging to various classes, for example, gallocatechins (Farhan et al. 2016a), curcumin (Ahsan and Hadi 1998), tannins (Khan and Hadi 1998), flavonoids (Said et al. 1992; Arif et al. 2015), resveratrol (Ahmad et al. 2000; Shamim et al. 2012), lead to DNA breakage either in absence or presence of copper ions. Copper is a fundamental metal ion found within chromatin and is known to be linked with DNA bases (Kagawa et al. 1991).

Fig. 1 Structure of gallic acid



Further, it has been reported that copper concentrations are well elevated in various malignancies (Gupte and Mumper 2009; Ebadi and Swanson 1988; Margalioth et al. 1987; Yoshida et al. 1993). Plant polyphenolics have both antioxidant and pro-oxidant properties (Hadi et al. 2000; Ebara et al. 2000; Inoue et al. 1994). Further, it has been earlier suggested that the prooxidant activity of plant polyphenols may be instrumental for their anticancer properties (Farhan et al. 2016a; Li and Trush 1994). Such a mechanism for the killing of cancer cells selectively of these polyphenols against cancer cells require endogenous copper, perhaps chromatin-bound copper and the subsequent prooxidant action. This can also help explain their selective cytotoxicity against cancer cells, with minimum to no effect against normal cells. The chemical structure of gallic acid is shown in Fig. 1.

DNA Damage Induced by Gallic Acid in Intact and Permeabilized Cells

It has been found in our laboratory as well as of the others that various groups of plant polyphenols are efficient of breaking DNA when treated with human lymphocytes. The damage can be viewed by Comet assay technique (Pool-Zobel et al. 1993). Using increasing concentrations of GA, we analyzed the capability to induce DNA breakage in isolated lymphocytes. A dose-based rise in DNA damage was observed (Fig. 2). As per our idea, polyphenolic compounds move chromatin-associated copper which results in breakage of DNA. We also found that tail formation in Comet assay caused by GA treatment was far more in case of permeabilized cells as compared to intact cells. It can be assumed that the capability of GA is to effectively associate with nuclei in a permeabilized cellular system.

Determination of DNA Damage by Gallic Acid Along with Metal Chelators in Intact and Permeabilized Cells

Metal chelators were utilized for copper, iron, and zinc to understand the involvement of the fore mentioned metals in DNA breakage by GA in intact and permeabilized cells. In case of intact cells neocuproine quenched DNA breakage. Neocuproine is known to be permeable to cell membrane which is a Cu(I)-specific chelator. On the other hand, zero

inhibition was noticed when a membrane-impermeable, Cu(I) chelator, bathocuproine was used. Desferrioxamine mesylate (iron chelator) as well as histidine (zinc chelator) were unsuccessful to interact. In contrast, copper chelators neocuproine/or bathocuproine interacted in permeabilized cell system. Specific chelators of iron and zinc failed to show effectiveness even in permeabilized cells system. These results implicated that copper associated with chromatin is mobilized by GA which leads to oxidative DNA damage.

Values represent DNA damage in cells (intact/or permeabilized) along with metal chelators as induced by GA compared as percentage to control (DNA breakage resulted by GA without chelator). Data shows mean ± SEM of three independently performed experiments. $^{2}P < 0.03$ when correlated with[1]. $^{3}P < 0.02$ when correlated with[2] (Table 1).

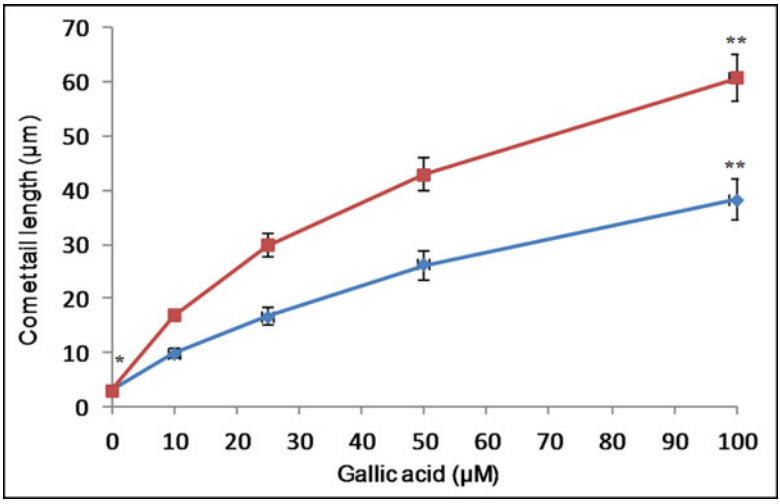


Fig. 2 A comparative figure of DNA breakage caused by GA in intact cells (blue line) and permeabilized cells (red line) with reference to comet tail lengths. The data reported is mean ± SEM of three independently conducted experiments. $p < 0.01$, when **values were correlated with *values

Table 1 Determination of metal chelators effect on gallic acid-induced DNA damage

	Cells (intact)		Cells (permeabilized)	
Dose	Tail length (µm)	Control (%)	Tail length (µm)	Control (%)
Gallic acid (50 µM)	26.44 ± 0.93^{1}	–	37.28 ± 1.57^{1}	–
+ Neocuproine (50 µM)	13.63 ± 0.87^{2}	48.44	14.33 ± 0.43^{3}	61.56
+ Bathocuproine (50 µM)	21.67 ± 0.41^{3}	18.04	8.68 ± 0.39^{3}	76.71
+ Histidine (50 µM)	22.65 ± 0.94^{3}	14.33	31.41 ± 1.27^{3}	15.74
+ Desferrioxamine mesylate (50 µM)	23.50 ± 1.11^{3}	11.11	30.53 ± 0.92^{3}	18.10

H_2O_2 Generation by Gallic Acid Inside Incubation Medium

Plant polyphenolics have a tendency to auto-oxidize when present in cell culture media leading in production of quinone and H_2O_2 that enter in cell nuclei and harm various macromolecules (Long et al. 2000). This effect results in the production of ROS that also leads to DNA breakage. We examined the production of H_2O_2 after the GA and correlated with tannic acid (TA) which is a well-established producer of H_2O_2 (Farhan et al. 2016b). The amount of formation of H_2O_2 by TA was much higher compared to GA suggesting that H_2O_2 is not accountable for DNA breakage in presence of GA treatment (Fig. 3).

Determination of Cell Growth by Gallic Acid in Human Breast Cancer Cells

We studied the effects of GA in human breast cancer cells (MDA-MB-231) and observed growth inhibition of MDA-MB-231 cells by GA in dose-based fashion (Fig. 4a). We also noticed human normal breast epithelial cells (MCF-10A) were unaffected to GA treatment. However, when supplemented to a copper-rich medium resulted in stimulation to GA action (Fig. 4b). The results obtained are in favor of our

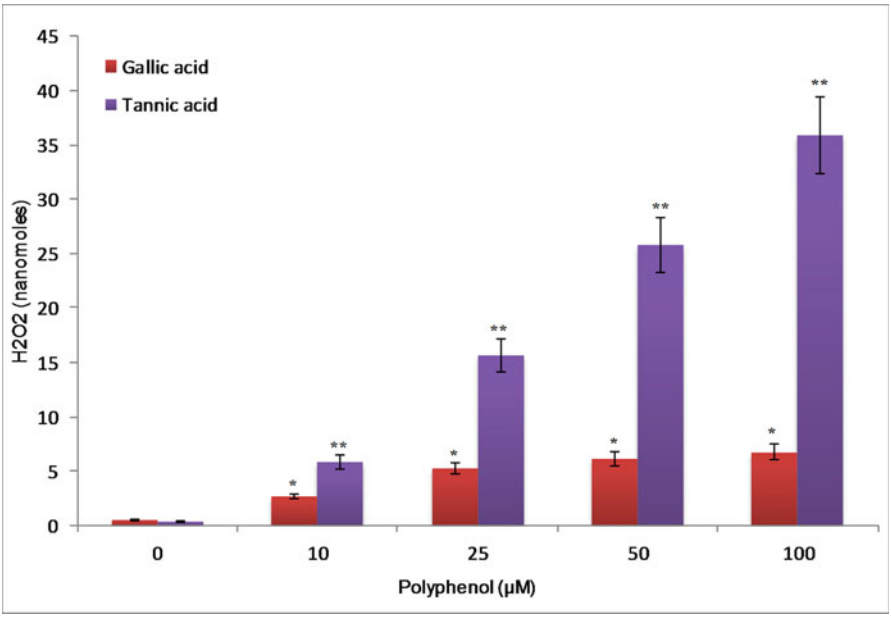
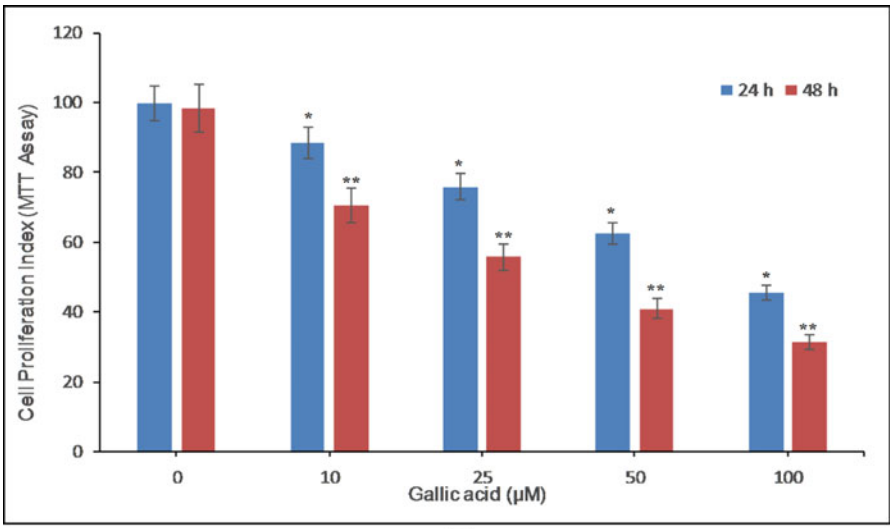
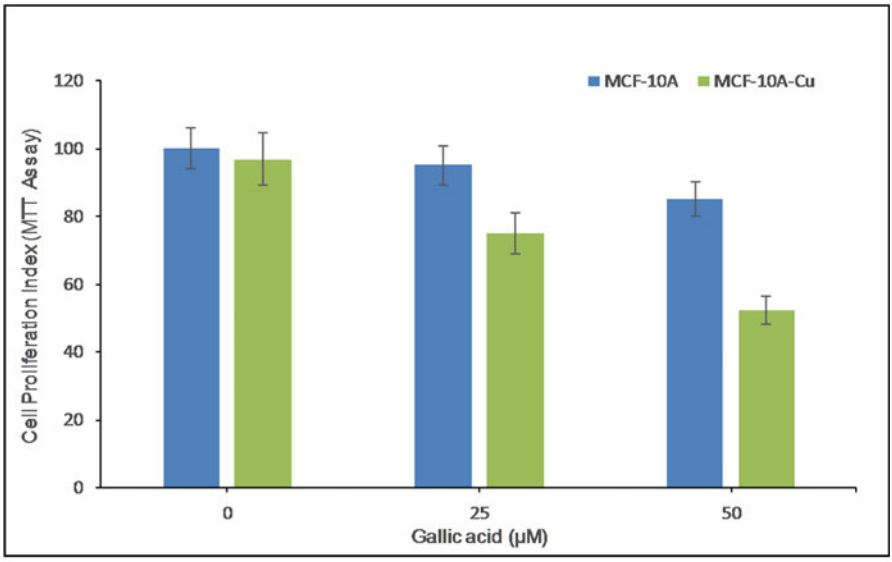


Fig. 3 The rate of H_2O_2 production (incubation medium) by TA and GA as measured by FOX assay. Values shown are mean ± SEM of three independently performed experiments. $p < 0.02$, when * values were correlated with ** values



(A)



(B)

Fig. 4 (**a**) The impact of GA was tested on the proliferation of MDA-MB-231 as observed by MTT assay. Using mentioned concentrations of GA, the cells were subjected to treatment for the time intervals 24 h and 48 h. The results procured are mentioned when compared to the control cells. (**b**) MCF-10A (human normal breast epithelial cells) and MCF-10A-Cu [MCF-10A cells enriched in copper (25 μM)] were treated with GA (0 μM, 25 μM, 50 μM) for 72 h. All values shown are % control mean ± SEM of three independently performed experiments. *$p < 0.03$ and **$p < 0.02$ when correlated with control (0 μM GA)

results published earlier focusing on the cancer chemopreventive action of plant polyphenols (Arif et al. 2015; Farhan et al. 2016b; Smith et al. 1992).

Gallic Acid and Cancer Chemoprevention

Over the years, many scientific researchers have utilized numerous varieties of cancer cell lines to investigate the prooxidant mechanism and cytotoxicity of plant polyphenols. In an effort to explain that normal cells remain unharmed during such action (Alyssa et al. 2013; Madlener et al. 2007; Agarwal et al. 2006; Quinlan and Gutteridge 1987), our analysis showcase that the selectively killing action of GA (or plant polyphenols) against cancer cells could be attributed to the prooxidant mechanism where GA is able to mobilize endogenic copper ions.

GA is a polyphenol that is relatively very well-absorbed (Khan et al. 2014). In a study (Wang et al. 2014) that compared the relative bioavailability of GA from acidum gallicum tablets versus brewed tea, it was found that GA from both sources was rapidly absorbed and metabolized. The mean maximum concentrations of plasma GA were 1.83 and 2.09 micromol/L from the tablets and tea, respectively. In addition, the highest concentrations of its metabolite in plasma were determined to be 2.83 and 2.64 micromol/L, respectively. Based on the available literature, it is believed that the plasma concentration of GA ranges between 2.2 and 9.9 microg/L (Manach et al. 2005). There is also evidence that the bioavailability of GA can be substantially improved by repeated doses. In a study conducted in mouse model (Shahrzad et al. 2001), it was shown that gavage administration of grape seed polyphenolic extract (GSPE) to mice could result in LC-MS detection of several key constituents of GSPE, with GA being a major one. Further, compared to a single acute dose, repeated doses significantly increased the bioavailability of GA and a 198% increase in plasma GA was observed.

A Copper-Dependent Anticancer Mechanism

The fact is that cellular, tissue, serum copper levels are increased in different types of cancers (Kaliora et al. 2013; Gupte and Mumper, 2009). Therefore, it may be safely assumed that malignant cells may be more susceptible to transfer of electron between GA (plant polyphenols) and copper ions to generate ROS. In the literature, we have sufficient data explaining the concentrations of Cu, Zn, Fe, and Se in patients suffering with cancer (Carpentieri et al. 1986; Bhadani et al. 2015). The most important point to consider is that the GA concentration needed for killing malignant cells selectively must be less than GA concentration required for killing normal cells. The same has been established that GA is cytotoxic to malignant cells rather than normal cells.

The distribution and metabolism of copper is overserved to be changed in tumor bearing humans, mice, and rats (Folkman 1972; Urso and Maffia 2015). Path-

breaking studies performed by Folkman (1971; Kuo et al. 2002) showed that copper is one of the simplest angiogenic molecules. Ceruloplasmin, tripeptide glycyl-histidyl-lysine, and heparin are copper-binding proteins playing crucial role in angiogenesis. The protein is known to be non-angiogenic when not bound with copper. However, when bound to copper, they become angiogenic (Zuo et al. 2006). The change in copper metabolism is currently a hot topic and seen as a major biomarker for molecular cancer imaging in cancer patients (Kaliora et al. 2013; Apelgot et al. 1986; Semczuk and Pomykalski 1973). In the goal to exploit copper's angiogenic potential as to evade cancer, copper chelators, for example, tetrathiomolybdate, clioquinol, etc., have shown to bring down tumor cells' growth both in vitro and in vivo (Wachsmann and Peng 2016; Singh et al. 2016; Jain et al. 2013; Fu et al. 2014; Fu et al. 2012; Crowe et al. 2013). It is also to be noted that copper has also been recognized to possess a pivotal role in intracellular signaling and tumor metastasis by engaging itself in transcriptional regulation of E-cadherin (Schimmer 2011).

Wolfe et al. (Pushie et al. 2014; Turski and Thiele 2009) have suggested a copper-driven Fenton reaction which suggests that generation of hydroxyl radicals is indeed efficient of causing apoptosis. The hydroxyl radical is found to be electrophilic possessing higher order reactivity. For that reason, it must possess a small radius of diffusion. To achieve DNA breakage, it must be generated close to cellular DNA (Wolfe et al. 1994). The position of the redox-active metals is particularly important as hydroxyl radical is highly reactive and interacts specially in closeness to the bound metal. Normal cells possess a balance between the antioxidant defense and free radical generation (Held et al. 1996; Pryor 1988). However, it is well corroborated that cells with tumor are under constant oxidative stress and possess a changed antioxidant system (Burkitt et al. 1996). Therefore, in malignant cell, additional ROS stress reaching up to the level of threshold could be the consequence for apoptosis (Kaliora et al. 2013). All the observations imply neoplastic cells are prone to oxidative stress as they deal with enhanced levels of ROS because of higher degree of metabolism and growth (Zhou et al. 2003).

Conclusion

Plant polyphenols are generally known to oppose the effects of ROS, preventing oxidative DNA breakage and ultimately lowering risks of cancer. During the course of time, newer studies focus on the findings that polyphenolic compounds can arbitrate ROS generation when various metal ions are present. The aforementioned prooxidant action may lead to apoptosis in malignant cells. Depending on the microenvironment inside the cell-based system, polyphenols may show either antioxidant/prooxidant action in nature. Copper, when available, plant polyphenols generally show prooxidant characteristics supplementing to the transition metal-redox cycling. The prooxidant action results in ROS-generated DNA breakage.

Future Direction

Plant polyphenols compounds are certainly adept of mobilizing as well as redox cycling nuclear copper leading ROS generation. This causes DNA breakage finally leading to cell death. The malignant cells are under constant ROS exposure produced by the redox activity of endogenous copper. The same can result into antioxidant behavior of cells promoting apoptosis. It is improbable to find one-shot therapy for diverse cancers. In recent times, studies on cancer relocated to the metabolism of cancer cells. In this scenario, our recommendations hold important value as they give strong ground for designing new cytotoxic agents which thereby target the cancer cells based on increased copper levels using gallic acid or plant polyphenols in general.

Conflict of Interest The authors declare no conflicts of interest.

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