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# Nanotherapeutics Of Gallic Acid For Cancer Therapy: A Mini Review

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***Abstract***
*The low solubility and absorption, around 40–70% of therapeutic compounds in clinical drug development, have bioavailability problems. Research shows that techniques based on nanotechnology can improve the pharmacokinetic characteristics of medications. Gallic acid (GA) is a member of the polyphenolic acid class. This study undertakes a comprehensive analysis of gallic acid (GA) encapsulated within gallic acid nanocarriers for cancer treatment, focusing on the advancements in nanoparticle technology that enhance GA's pharmacological activities by overcoming its systemic clearance and bioavailability limitations, thereby optimizing its anticancer activity. These approaches allow for better modulation of important cancer-related pathways such as PI3K/Akt and NF-κB, controlled release, and less toxicity. This review focuses on the molecular mechanisms, transport methods, and clinical translation potential of GA-loaded nanocarriers in cancer therapy.*
***Keywords:*** *Gallic acid, Nanocarriers, Anticancer, polyphenolic acid*

## INTRODUCTION

After cardiovascular illnesses, cancer is a significant cause of mortality globally and is a non-communicable disease [1]. Because cancer incidence is closely linked to aging, it is the most significant obstacle to extending life expectancy. In both developed and developing nations, managing and treating cancer is a significant issue for medical professionals. Treatment for cancer necessitates meticulous planning, therapeutic approaches, and schedules [2]. Despite a notable increase in the number of cancer survivors in the United States, cancer continues to have high mortality and morbidity rates. Furthermore, some lifestyle modifications, such as quitting smoking, have contributed to a decrease in the number of deaths from cancer [3]. Among other characteristics, cancer cells differ from healthy cells in several ways, including genetics, growth and migratory patterns, and responsiveness to therapy. Each form of cancer has distinct standard treatment choices, but the most common arsenal includes surgery, chemotherapy, and radiation. The ability of cancer cells to penetrate surrounding tissues and be transported to distant organs frequently limits the efficacy of surgery [4]. Surgery cannot eradicate all cancer cells because they might spread to different parts of the body, especially when the disease is more advanced. Furthermore, surgery is an intrusive procedure, and it is not always advised to use it. On the other hand, advanced cancer cells cannot be effectively suppressed by chemotherapy or radiation therapy [5]. The key goal of cancer research is to develop novel anti-tumor drugs that are highly effective in inhibiting tumor growth and metastasis while minimizing toxicity. In addition to causing adverse effects and therapeutic resistance, the existing arsenal of synthetic medicines with anti-tumor properties is also costly for the average person [6]. Gallic acid, a plant-derived phenolic compound, is commonly recognized for its anticancer, antioxidant, and antibacterial properties. Its ability to neutralize free radicals has been widely recognized, particularly for its role in preventing chemically induced carcinogenesis by mitigating oxidative stress and cellular damage [7-8]. 3, 4, 5-trihydroxybenzoic acid, a phenolic molecule called gallic acid, is naturally found in sources such as oak barks, tea leaves, and gallnuts. This crystalline solid has a melting point of about 210°C and the molecular mass is 170.12 grams per mol [9].

**The Origin -**Many plants, including Dillenia indica, Syzygium cordatum, Oenothera bienni, Vitis vinifera, floribunda, Psidium guajava, Toona sinensis, Caesalpinia sappan, Hamamelis virginiana, Rubus

suavissimus, and Allan blackia. The chemical formula of GA is $C_6H_2(OH)3CO_2H$ and its molecular weight is 170.12 gram per mol. GA, due to the fact that it has more hydroxyl groups at present, is unstable in the presence of light, heat, and pH [10].

**ROLE OF PI3K/AKT SIGNALING PATHWAY GALLIC ACID IN CANCER**

The PI3K/Akt signaling pathway is essential for controlling cell survival and proliferation, is effectively inhibited by gallic acid (GA), thereby disrupting processes essential for tumor growth and progression. GA suppresses tumor development and encourages apoptosis by downregulating this mechanism. This action is frequently combined with NF-κB signaling suppression, which intensifies apoptotic processes [11]. By triggering the p38 MAPK pathway, which is implicated in stress-induced apoptosis, GA enhances apoptosis through the downstream protein phosphorylation, which eventually results in cell death [12].

**POLYMERIC NANOPARTICLE USED FOR GA DELIVERY**

Polymeric nanoparticles, such as those made from poly(lactic-co-glycolic acid), chitosan, and polyethylene glycol (PEG) are commonly used to transport GA. These nanoparticles have the capacity to regulate medication release and are biocompatible and biodegradable. Achieving substantial drug loading while maintaining the nanoparticles' stability and guaranteeing homogenous particle size are obstacles, albeit [13]. Both hydrophilic and hydrophobic medications are encapsulated in lipid-based nanoparticles, which includes solid lipid and liposomes [14], which provide defense against enzymatic deterioration. A robust matrix provided by SLNs helps improve stability and control GA delivery. Low loading capacity and drug leakage are two problems that these systems may encounter [15]. Gold, silica, or iron oxide are examples of inorganic nanoparticles that have special qualities including improved imaging capabilities and magnetic responsiveness. Although the distribution and release of GA can be enhanced by engineering these nanoparticles, issues with long-term toxicity and biocompatibility must be resolved.

**Biomarker of Anticancer properties of gallic acid**

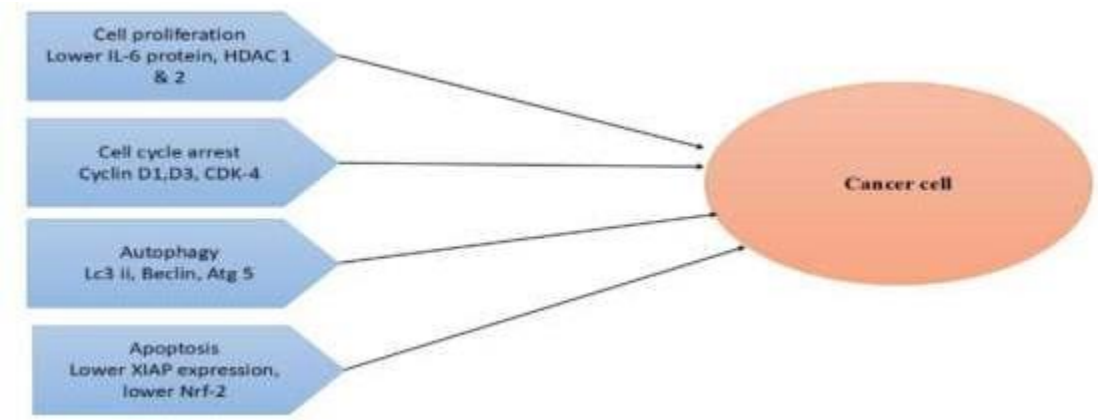


Fig. (1). Various cellular biomarkers in anticancer activity of Gallic Acid.

**ADVANCED MEDICATION DELIVERY METHODS FOR ENHANCED GALLIC ACID BIOPHARMACEUTICAL PROPERTIES**

**Liang et al. (2012)** examined the anticancer effects of GA on MNNG/HOS and U-2OS osteosarcoma cell lines. Cumulative MTT and V-FITC/PI double labeling tests were performed in this study to evaluate GA's ability to induce apoptosis and cell proliferation. These results confirmed that GA exerted apoptotic and antiproliferative activities through the upstream of p-38 and downstream of ERK1/2 and JNK. To further investigate GA's impact in vivo, MNNG/HOS xenograft tumors were established in BALB/c nude mice. The finding demonstrated that GA administration suppressed xenograft tumor growth in a manner dependent on the dosage given. Also, after GA dosage, an immunohistochemistry examination of MNNG/HOS osteosarcoma tissue showed the apoptotic activity occurring upstream inhibition of the PCNA and CD31 expression [16].

**Wang et al. (2016)** Using SCLC H446 cells, showed the antitumor activity of GA and its positive impacts on cisplatin's anticancer activity. GA's reduced apoptotic activity and cell survival were demonstrated by the FITC/PI staining and in vitro MTT test, respectively. Furthermore, the activation

of proteins linked to mitochondrial apoptosis was validated by western blotting data. Analyzed under an inverted microscope, the effects of GA and cisplatin on H466 cells revealed altered morphology, growth suppression, and apoptosis, which were explained by ROS activation, MMP disruption, and XIAP expression inhibition [17].

**NANO-EMULSION**

Droplet size in liquid-in-liquid dispersions is approximately 100nm, which are kinetically stable are called nanoemssulsions [18].

**Costa et al. (2019)** The goal was to demonstrate that the emulsion droplet size is not influenced by interfacial concentrations of antioxidants. The authors created and described nano-emulsions of fish and olive oils in water using different droplet sizes. According to in vitro kinetic investigations, the oxidative stability of the lipids remains the same when droplet size varies in the absence of GA [19]

**SOLID LIPID NANOPARTICLES**

**Cordova et al. (2017)** illustrated the anti-cancer effectiveness of gallic acid derivative (G8) encapsulated solid lipid nanoparticles produced using the hot homogenization technique in a lung metastasis model. When given GA and G8-NVM, Swiss albino mice with metastases showed fewer metastases showed less metastasis in vivo. G8-NVM is found to have lower toxicological parameters than free drugs, including biochemical and hematological parameters, weight fluctuations, histological examinations, and oxidative status in the liver [20].

**Consoli et al. (2016)** employed the spray chilling approach, solid lipid microparticles (SLMs) loaded with gallic acid are created utilizing soybean oil (SO) and fully hydrogenated soybean oil (FSHO) as wall material. Depending on the lipid blend content, the particles varied in size from 24 to 36 μm, and their size reduced as the amount of FSHO rose. A smooth, spherical form with fat crystals connected was shown by SEM data [21].

**POLYMERIC NANOCARRIERS FOR CONTROLLED GA DELIVERY: DEVELOPMENT, CHARACTERIZATION, AND THERAPEUTIC POTENTIAL**

**Behl et al. (2013)** reported the evolution and characterisation of antioxidant gallic acid loaded polymeric nanoparticles as shown in Table 1. The biodegradable properties of nanogels are evidenced by their disintegration in the presence of glutathione. Finding from the FRAP and DPPH assays indicate that the in vitro release characteristics reveal a nanoparticle formulation that exhibits controlled release without compromising its antioxidant efficacy. The DCFHDA and MTT assays were employed to assess biocompatibility. Furthermore, it was established that the nanogel demonstrates efficacy in scavenging free radicals within a cellular environment [22].

**Dorniani et al. (2014)** through the application of physicochemical characterization methodologies, Fe3O4 nanoparticles were synthesized and subsequently covered them with polyvinyl alcohol GA (FPVAG) and polyethylene glycol-GA (FPEGG), followed by an evaluation of their efficacy. The characterization of Fe3O4 nanoparticles revealed a spherical morphology with a diameter of 9nm by X-ray diffraction and transmission electron microscopy (TEM), in contrast to diameters of 31nm and 35 nm when encapsulated with the polymers polyethylene glycol (PEG) and polyvinyl alcohol (PVA), respectively. Successful formation of nanoparticles with gallic acid as the active medication after PVA and PEG coating is demonstrated by magnetic measurements and FTIR. After encapsulating the nanoparticles, thermogravimetric analysis demonstrates improved thermal stability [23].

**Jin et al. (2017)** the synthesis of Fe-GA-PEG CNPs was shown to exhibited remarkable stability, and both magnetic resonance imaging (MRI) and in vivo photoacoustic tomography (PAT) of the nanostructure following intravenous delivery demonstrated possible passive tumour targeting. Additionally, Fe-GA-PEG CNPs are chelator-free labelled with 64Cu for PET imaging, confirming the formulation's significant tumour absorption. After intravenous injection combined with laser irradiation, additional results indicate that Fe-GA-PEG CNPs may have anti-tumor properties [24].

**Lamarra et al. (2019)** The goal of was to use the thermocompression technique to create a nanocomposite bilayer system made up of polyvinyl alcohol (PVA) films and chitosan nanocomposites carrying GA. The outcomes of SEM, FTIR, and DSC analyses validate the interactions among a system's layers. The medicine is shielded from water vapor, oxygen, and UV deterioration by the barrier that

makes up the prepared system. As a result, this system may be utilized as a material for packaging that has better antioxidant qualities [25].

Table 1. Certain polymeric nanocarriers used for GA delivery

| **Gallic acid delivery system** | **Physico-chemical properties** | **Technique to prepare GA nanoparticles** |
|---|---|---|
| Chitosan | The NPs have a particle size of 104.40 ± 1.69 and a zeta potential of 39.67 ± 3.66mV. | Ionotropic gelation method |
| PEG | The particles measured between 227 ± 51.78 nm and 573.3 ± 207.02 nm in size, exhibited a loading efficiency of 60–70%, and showed a controlled release pattern, contributing to their biocompatibility. | Aqueous inverse mini emulsion using ATRP |
| BSA | Enhanced biocompatibility with 3.5nm size of NPs | BSA-assisted Biomineralization method |
| PLGA-CS-PEG | EE of almost 80% and sustained release characteristics | Single emulsion solvent evaporation method |
| Alginate-chitosan | Size range of 100–200 nm with 96% yield | Ionic gelation method |

## ANTICANCER PROPERTIES OF POLYMER NANOPARTICLES MADE OF BIOACTIVE PEPTIDES AND GALLIC ACID- GRAFTED CHITOSAN

Gallic acid (GA) grafted chitosan (CS, GA-g-CS for GA grafted CS) and caseino phosphor peptides (CPP) were used to make polymer nanoparticles that would deliver (−)-epigallocatechin-3-gallate as novel functional foods [26]. From 26.5 ± 1.0 to 126.0 ± 1.1 mg/g, the quantities of GA in GA-g-CS copolymers varied as the molar ratio of GA to glucosamine in CS increased. GA-g-CS was much more soluble in neutral and alkaline conditions than CS. The combination of GA-g-CS and CPP resulted in stable, spherical nanoparticles with a zeta potential below +30 mV and a particle size of 300nm, exhibiting significant cytotoxicity and antioxidant activities against Caco-2 colon cancer cells [27].

## GALLIC ACID-CAPPED GOLD NANOPARTICLES

Distant metastasis is more common in triple-negative breast tumors (TNBCs), which are also more invasive. An essential part of TNBC metastasis is MMP-9 and a malignant progression driven by EGF/EGFR [28]. Several studies have shown that the anti-tumor effect of phytochemical substances is enhanced when they are conjugated with gold nanoparticles (AuNPs). Alternatively, gallic acid treatment results in decreased expression of MMP-9 in cancer cells. Consequently, the current study investigated how GA-capped AuNPs (GA-AuNPs) affected the expression of MMP-9 in TNBC MDA-MB-231 cells that were treated with EGF. Gallic acid gold nanoparticles, which were spherical and had an average diameter of about 50nm, were created by the so-called "green synthesis" of gold nanoparticles using GA at pH 10. Significantly, gallic acid gold nanoparticles suppressed the up-regulation of MMP-9 induced by EGF, as well as the invasion and migration of EGF-treated cells [29]. When GA-AuNPs suppressed Akt/p65 and ERK/c-Jun phosphorylation in EGF- treated cells, MMP-9 mRNA and protein levels were down-regulated. GA-AuNPs reduced the p300 protein's EGF-promoted stability, whereas EGF-induced p300 stabilisation was found to be crucial for the synthesis of MMP-9 [30]. Gallic acid required a dose approximately 100 times greater than that of GA-AuNPs to similarly inhibit MMP-9 production in cells treated with EGF, despite both substances preventing EGF-induced MMP-9 up-regulation through the same signaling pathway. GA-AuNPs more effectively reduce EGF/EGFR-mediated MMP-9 synthesis in TNBC MDA-MB-231 cells compared to gallic acid, suggesting a potential method to enhance the anti-tumor effects of GA. [31].

## CONCLUSION

GA-loaded nanoparticles enhanced stability, decreased toxicity to the body, and controlled release properties make them highly promising for the treatment of cancer. In cancer treatment, GA in conjunction with other pharmacological compound is a successful tactic that amplifies the synergistic effects of combination medicinal agents. GA co-delivery has several advantages in the treatment of cancer. In order to increase GA's bioavailability by nanoparticle encapsulation, a number of issues pertaining to drug loading efficiency, surface charge, and particle size must be resolved. Furthermore, it may be simple to scale up and replicate the synthetic processes employed to manufacture these nanoparticles. Because GA possesses a variety of anti-cancer properties, it is more effective than other nanoparticles filled with natural chemicals. GA's potential in treating cancer is increased when it is used in conjunction with other therapeutic medicines.

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