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Gallic acid: A phyto-phenol role in tumor management with photosensitizing agent as targeting moiety

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Abstract
Gallic acid (3, 4, 5-trihydroxybenzoic acid) a naturally occurring low molecular weight triphenolic compound. which have been used as effectual agent for treating many illnesses from ancient times. In the present scenario the uses of polyphenolic compounds have been widely increased due to its enomorous significant activity and were the commercial drugs are carrying a huge burden of side effects in cancer management. Moreover for complete eradication and to shun resistance by other conventional therapy in tumor cells a novel co-therapy is needed. Recently a co-therapy Photodynamic therapy playing a several role in cancer treatment which has a small number of short term side effects and have high localization on tumor cells. This co-therapy may increase the synergistic effect of polyphenols on tumor cells and use to promote high antioxidant effect on normal cells and also suppose to inhibit angiogenesis process and activate our own immune response toward tumor cells. In future it would be a most promising co-therapy with polyphenols to treat all kind of solid tumors.

Keywords: Gallic acid, photodynamic therapy, cancer management

1. Introduction
Gallic acid, a naturally occurring plant phenolic compound, is present in a wide variety of plant-based foods. Gallic acid is one of the major active component of Chinese gall, and is widely distributed in natural herbal plants and in large amounts of prescribed Chinese herbs [1]. Gallic acid derivatives have also been found in a number of phytomedicines with diverse biological and pharmacological activities, including radical scavenging, interfering with the cell signaling pathways and apoptosis of cancer cells

The anticancer activity of GA is related to the induction of apoptosis through different mechanisms like generation of reactive oxygen species (ROS), regulation of apoptotic and anti-apoptotic proteins, suppression and promotion of oncogenes, inhibition of matrix metalloproteinases (MMPs) and cell cycle arrest depending upon the type of cancer investigated [2].

The ideal cancer treatment should both destroy the primary tumor and at the same time educate the immune system to recognize the tumor as foreign so that distant metastases will also be eradicated. PDT by its effects on tumor cells and on tumor vessels as well as by the activation of the host's immunitary cells is among the modern non-invasive methods of anti-tumor treatment [3].

PDT involves the administration of a photosensitizing agent (PS) and the exposure of the tumor to light with an adequate wavelength so that the photosensitizer would pass in an excited singlet. From this state the PS can pass in a triplet state in which it interacts either with the moleculasr oxygen generating singlet oxygen (O2) or with the biomolecules in the tissues producing radical forms of the PS [4]. These reactive forms, by their reaction with oxygen, generate hydroxyl radical, hydrogen peroxide and superoxide anion. which in their turn oxidize the macromolecules in the cells and compromise the cell function or even determine cell death by apoptosis or necrosis

PDT also affects endothelial cells of tumor vessels resulting vascular damage. In addition to this direct killing process, tumor eradication also arises from an acute inflammatory response featured by an increased level of various mediators in the PDT-treated tumor area (IL-1 β, G-CSF, IL- 8, MIP–2)

2. Pharmacological activity of gallic acid
There are several reports for the pharmacological activities of gallic acid and its derivatives. Review of literature reveals hepatoprotective potential of gallic acid in alleviating paracetamol-induced liver damage in mice, hepatic ischemia reperfusion injury in rats, CCl4 -induced acute liver injury in rats, sodium fluoride-induced oxidative stress, acute liver damage induced by CCl4, N nitroso-compounds-induced mutagenicity as well as obviating mouse lung adenomas by amines or ureas plus nitrite and by nitroso compounds.

GA has been reported to suppress cell viability, proliferation, invasion and angiogenesis in human glioma cells, inhibits the growth of HeLa cervical cancer cells via apoptosis and necrosis, induces apoptosis in tumoral cell lines and inhibit lymphocyte proliferation, inhibits rib nucleotide reductase and cyclooxygenases in human HL-60 promyelocytic leukemia cells, causes inactivating phosphorylation via ATM-Chk2 activation, leading to cell cycle arrest. It is also reported to possess anti-oxidant activity.

It has been reported that GA has anti-microbial activity against methicillin-resistant Staphylococcus aureus and Helicobacter pylori. Anti-inflammatory actitivity has been evaluated by zymosan induced acute food pad swelling in

mice, carrageenan-induced paw edema, acetic acid-induced writhing responses and formalin-induced pain in animal models as reported in numerous publications and the suggested mechanisms were scavenging of superoxide anions, inhibition of myeloperoxidase release and activity as well as interference with activity of NADPH-oxidase.

The other reported activities are anti depressant, antiparkinson, anti-diabetic, anti-malarial, diuretic, cardioprotective, anti-viral, antifungal, wound healing, anthelmintic and anxiolytic. Gallic acid, when combine with other natural products such as, calycosin, reported to synergistically attenuate neutrophil infiltration and subsequent injury in isoproterenol-induced myocardial infarction

3. Gallic acid in cancer [5]

GA was capable of inhibiting the proliferation of cells in a time and dose-dependent manner, as well as inducing the apoptosis of cells. GA induced caspase-3, caspase-9 and reactive oxygen species activity, elevated the expression of apoptosis regulator Bcl-2-like protein 4 and reduced the mitochondrial membrane potential in cells.

Gallic acid and its derivatives – cancer cell- mitochondria – increase ROS – decrease MMP – release and activation of caspase 3, 8, 9- apoptosis

Gallic acid and its derivatives- cancer cell- DNA fragmentation- increase Bax genes- decrease Bcl-2 genes – increase activation of NF – cell cycle arrest – apoptosis

Gallic acid and its derivatives – ICAM-1, VCAM-1- metastatis, invasion and angiogenesis – increase RhoA, RhoB- cell cycle arrest- apoptosis

Gallic acid – cancer cell- inhibition of MMP- cell cycle arrest- apoptosis

4. Photodynamic therapy

Photodynamic therapy (PDT) is a treatment that uses special drugs, called photosensitizing agents, along with light to kill cancer cells. The drugs only work after they have been activated or “turned on” by certain kinds of light. PDT may also be called hotoradiation therapy, phototherapy, or photochemotherapy.

PDT has several potential advantages over surgery and radiotherapy:

- It is comparatively non-invasive
- It can be targeted accurately
- Repeated doses can be given without the total-dose limitations associated with radiotherapy, and the healing process results in little or no scarring.
- PDT can usually be done in an outpatient or day-case setting, is convenient for the patient, and has no side-effects.

Process of photodynamic therapy

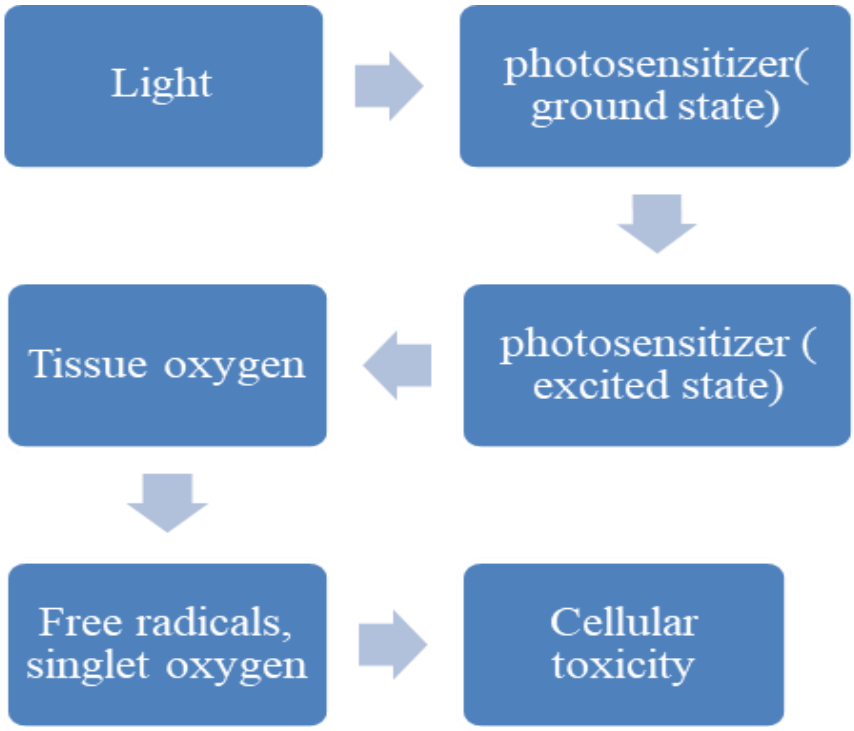

Fig 1: Photodynamic therapy on cancer cell

4.1 Mechanism of action of PDT [6]

PDT involves the administration of a photosensitizing agent into the tissue of a tumor, followed by the activation of this agent using light at a specific wavelength.

The treatment consists of two stages

First stage: The photosensitizing agent is accumulated, particularly in the tumor cells, following topical or systemic administration.

Second stage: The photosensitized tumor is exposed to light at a wavelength that coincides with the absorption spectrum

of the photosensitizing agent.
This activated agent transfers energy to molecular oxygen, generating reactive oxygen species (ROS).
The subsequent oxidation of the lipids, amino-acids and proteins induces necrosis and apoptosis. In addition, ROS indirectly stimulate the transcription and release of inflammatory mediators. Oxidation of the cell constituents by ROS damages the plasma membranes and the cell organelles, with a subsequent alteration in permeability and transport function between the intra- and extracellular media. Inhibition of mitochondrial enzymes appears to represent a key event in cell death by PDT.

4.2 An apoptotic response to PDT
This response may be directly induced by PDT without any need for the transduction of intermediary signs that may be lacking in certain drug resistant neoplastic cells. Cell death by PDT does not appear to depend on the phase of the cell cycle or on genetic factor.
PDT targets include tumor cells, tissue microvasculature and the host's inflammatory and immune systems [7]. It appears clear that the combination of all these components is required in order to achieve long term control of the tumor. The principal characteristic of the inflammatory process is the release of vasoactive substances, components of the complement, proteinases, peroxidases, cytokines, growth factors and other immuno-regulators. There is evidence of an increase in the regulation of interleukin 1 beta (IL-1beta), interleukin 2 (IL-2), tumor necrosis factor alpha (TNF alpha) and granulocyte colony-stimulating factor (G-CSF)

4.3 Light sources for PDT [8]
Various light sources may be used in topical PDT. Maximum light absorption by porphyrins is close to 405 nm. This range of maximum absorption is referred to as the Soret Band. Other lower peaks of absorption, referred to as Q-bands, are found at 510, 545, 580 and 630 nm.
The majority of clinical studies are performed using light wavelengths of 625 to 633 nm, which permit greater skin penetration.

The light sources available for PDT belong to three major groups
1. Broad spectrum
2. Diode lamp
3. Lasers

The non-coherent light sources described in clinical studies on PDT include the halogen lamps used in slide projectors, light-emitting-diode (LED) lamps and, more recently, intense pulsed light (IPL). Currently, the variety of sources emitting noncoherent light is enormous, with a spectrum of light emission that coincides with the absorption peaks of Pp IX. Light with wavelengths of 635 nm is capable of penetrating the skin to a depth of approximately 6 mm compared to 1-2 mm with a wavelength of 400- 500 nm. The effective therapeutic depth, nevertheless, appears to be close to 1-3 mm when 635 nm is used. This is due to the capacity to produce a photodynamic reaction, which depends on the dose of light and also on the quantity of photosensitizer used in the target tissue
Lasers present a specific wavelength that corresponds to the peak absorption of the photosensitizer. Its capacity to emit high flux monochromatic light, associated with its focal precision, allows small lesions to be treated with minimal damage to the surrounding tissue and within a short time interval [9]. Nevertheless, for the treatment of dermatological conditions using PDT and protoporphyrin-based sensitizers, lasers show no advantage over cheaper and more practical equipment options such as non-coherent light sources [10]. These sources emit a large radiation field, enabling larger areas of the skin surface to be treated.

5 Combinations of PDT with other therapies
Two general approaches may increase antitumor effectiveness of PDT: (i) sensitization of tumor cells to PDT; and (ii) interference with cytoprotective molecular responses triggered by PDT in surviving tumor or stromal cells. Any interactions between PDT and PDT-sensitizing agents will be confined to the illuminated area. Therefore, the potentiated toxicity of the combinations is not systemic. This should be of special importance in elderly or debilitated patients who tolerate more intensive therapeutic regimes poorly. Moreover, considering its unique $^1O_2$-dependent cytotoxic effects, PDT can be safely combined with other antitumor treatments without the risk of inducing cross-resistance
There have been few studies on combinations of PDT with standard antitumor regimens. PDT can be used in combination with surgery as a neoadjuvant, adjuvant or repetitive adjuvant treatment, preferably fluorescence image-guided to confine illumination to the most suspicious lesions. PDT has also been successfully combined with radiotherapy and chemotherapy

6. Polyhenols with PDT
The major treatment for cancer is chemotherapy, radiotherapy and surgery. Chemotherapy has good results toward cancer cell but still it has lack of specificity and side effects. The radiotherapy can give based on the stage of cancer and can suggest with chemotherapy and after surgery too. Even though it is in practice for more than a decade's it had enormous side effects such as fatigue, loss of appetite, heavy pain during the treatment and after the treatment, alopecia, heavy damage of normal cells, decolorization of skin even sometimes the skin may peel off, hospitalization etc. In surgery more frequently lymphodema, seroma may occur and take long time to cure and also difficulty if cancer cells are grown behond the site. However, use of this technology requires further improvements as tumor recurrences can occur. This may be due to the increase of cyclooxygenase (COX)-2, HIF-1α, or VEGF gene expression. Recently, it has been shown that inhibitors of cyclooxygenase (COX)-2, HIF-1α, or VEGF can be effective in combination with PDT therapy and polyphenols.

7. Adverse reactions and current limitations of PDT

Compared to surgery or radiation therapy, PDT is less invasive and adverse reactions are relatively mild and not long-lasting. Depending on the PS and the therapeutic protocol, adverse events associated with PDT include photosensitivity, erythema, edema, fever, pleural effusion, constipation, anemia and respiratory insufficiency. The principal side effect of PDT is pain, which usually occurs in the early part of irradiation and then gradually decreases over time. The mechanism of PDT-induced pain is not well understood, but in most cases it can be well controlled by a combination of opiate, opioid and no steroidal anti-inflammatory drugs. Photosensitivity is another common complication, which can last for months. In the majority of cases it is mild-to-moderate and requires no treatment. Photophobia, visual discomfort and dyschromias are also listed among the side effects of PDT. It is important to stress that most side effects can be alleviated by the proper selection of the type of PS and PS dosage, parameters of illumination and other details of the PDT treatment protocol. Standardization of the treatment protocols and prediction of the PDT response, however, are seriously hampered by the lack of established PDT dosimetry. In contrast to ionizing radiation, no agreement has been reached on how the doses of PS and light should be measured, and even no widely accepted definition of dose exists. In addition, the optimum PS and light doses as well as drug-light time interval may vary from patient to patient or lesion to lesion, which prevents the application of standardized protocols and the achievement of highest response rates.

Among the limitations of PSs currently used for clinical PDT are the difficulty in treating large tumor masses and the limited depth of treatment. Visible light can penetrate the tissues not deeper than 5-10 mm, which restricts the application of PDT to mainly superficial lesions. A detailed description of the current state of PDT and its limitations can be found in comprehensive reviews

Cancer are currently treated with PDT [11]

To date, the FDA has approved the photosensitizing agent called porfimer sodium, or Photofrin, for use in PDT to treat or relieve the symptoms of esophageal cancer and non-small cell lung cancer. Porfimer sodium is approved to relieve symptoms of esophageal cancer when the cancer obstructs the esophagus or when the cancer cannot be satisfactorily treated with laser therapy alone. Porfimer sodium is used to treat non-small cell lung cancer in patients for whom the usual treatments are not appropriate, and to relieve symptoms in patients with non-small cell lung cancer that obstructs the airways. In 2003, the FDA approved porfimer sodium for the treatment of precancerous lesions in patients with Barrett esophagus, a condition that can lead to esophageal cancer.

8 Strategies for perfecting PDT

The development of better, more efficient compounds, free of the shortcomings of the first- and second-generation PSs, is among the primary strategies for improving PDT. This includes synthesis of PSs with strong absorption bands in the NIR region of the spectrum, which overcomes one of the main limitations of the currently clinically approved PSs - the insufficient depth of treatment. Improvement of PSs can be aided by the latest advances in nanotechnology. Nanoparticles have been used as PSs themselves, for delivery of PSs or as energy transducers. Targeted delivery of PSs is achieved by conjugation with antibodies, engineered synthesis of molecules with specific structure and even by attachment of PSs to magnetic nanoparticles. In the latter case, an externally applied magnetic field directs the PS to the lesion. Attachment of different modules to PSs, for example DNA- or peptide-based linkers and cancer cell-specific delivery vehicles, is used to improve both target specificity and pharmacological properties. In addition to the efforts in developing better PSs, various strategies driven by the current understanding of photo physics, photochemistry, photobiology and the latest technological advances have been evolved to meet the requirements for effective PDT outcome. Deep treatment, using PSs absorbing in the NIR region of the spectrum, is achieved by two-photon PDT. It is based on the development of laser technology, which allows the application of short (approx. 100 fs) laser pulses with high peak power. Instead of one, two light photons are absorbed and each photon accounts for only half of the excitation energy. Metronomic PDT is based on the application of very low doses of PSs combined with low rates of irradiation lasting for extended periods of time. As mentioned before, the outcome is cell death by apoptosis with minimal tissue necrosis.

Irrespective of the advances in laser technology, synthetic chemistry, nanotechnology and photobiology, PDT, more than a quarter of a century after its first clinical approval, is still not accepted as ‘standard' therapy even in areas of medicine where real improvement in outcome using standard therapy has not been achieved. The solution of this problem has been summarized by Moghissi, who recommends that, in order to overcome the current challenges and rise to the height of its potential, PDT needs commitment and funds

8.1 FDA and photodynamic therapy [12]

The US Food and Drug Administration (FDA) approved the use of photodynamic therapy in the treatment of severe acne in the year 2003. The administration also approved the use of the photo-sensitizing agent, Photofrin, for the treatment of esophageal cancer and non-small lung cancer. This agent relieves the symptoms of esophageal cancer and is helpful in treating cancers that don't respond to other treatments.

Photofrin was also approved for the treatment of pre-cancerous lesions in patients suffering from Barrett's esophagus. Other photo-sensitizing agents that have also been approved by the FDA are Levulan and Metvixia cream. Levulan is activated by blue light and has been approved for use on the face and scalp areas. It's used in the treatment of actinic keratosis and skin lymphomas such as mycosis fungoides. Metvixia is activated with red light and is used to treat non-hyperkeratotic actinic keratoses of the face and the scalp.

8.2 New photosensitizers in clinical trials [13]

8.2.1 Tin Etiopurpurin, SnET2 (Purlytin)

SnET2, a chlorin photosensitizer developed by Miravant Inc. (formerly PDT Inc., Santa Barbara, CA) currently is in phase II trials aimed at the U.S. FDA approval for cutaneous metastatic breast cancer and Kaposi's sarcoma in patients with acquired immunodeficiency syndrome.

8.2.2 Lutetium Texaphyrin (Lu-tex)

A phase II/III trial using Lu-tex is about to begin for treatment of certain skin lesions. A preliminary report has described some results from phase I trials involving various skin lesions (15 breast metastases, seven malignant melanomas, five Kaposi's sarcomas, and two invasive basal cell and two squamous cell carcinomas).

8.2.3 Benzoporphyrin Derivative-Monoacid Ring A (BPD-MA)

BPD-MA has been in phase I/II trials for treatment of skin cancers but perhaps the most interesting application is the treatment of age-related macular degeneration, the commonest cause of blindness in people over the age of 50 years [14]. In one form, it is characterized by leaky neovascularization near the macula that impairs vision. Current treatment involves the use of thermal lasers which can result in damage of the overlying retina with further loss of sight. With PDT, BPD-MA is infused and shortly thereafter, when the drug is confined to the vessels as much as possible, the drug is activated at 690 nm through an ophthalmoscope generally using a diode laser.

8.2.4 Tetra (m-hydroxyphenyl) chlorin, mTHPC (Foscan)

This chlorin photosensitizer is undergoing clinical trials for head and neck cancer in Europe and the United States under the sponsorship of Scotia Pharmaceutical (Great Britain). This material appears to be the most active of all photosensitizers studied to date, requiring only very low drug doses (as little as 0.1 mg/kg) and light doses (as low as 10 J/cm^2) for efficacy.

8.2.5 N-Aspartyl Chlorin e6 (NPe6)

NPe6 is undergoing clinical trials in Japan under the sponsorship of Nippon Petrochemicals for treatment of endobronchial lung cancer. Results of this trial are not available at this time. Previous reports using NPe6 in skin cancers have shown it to be an effective photosensitizer with little or no long term cutaneous photosensitivity.

Conclusion

Gallic acid and its derivatives are considered as a potent drug for cancer treatment and also as well as in combination with other anticancer drugs may increase the efficiency of chemotherapy. In recent years Gallic acid with a co-therpy called photodynamic therapy are believed to increase the synergistic activity of gallic acid on cancer cell and also the photosensitizing agent with gallic acid may increase the ROS production in cancer cell and increase the percentage of death rate. Moreover gallic acid is considered has a potent antioxidant agent for more than a decade's so thereby which can reduce the side effects caused by normal cell damage by laser light and also may reduce the rate of infection after surgery has it had antimicrobial properties. So other than anticancer activity its enomorous pharmacological activity made the molecules has a lead promising molecule for cancer therapy. However there is still a need for more experimentation in knock-out animal models and human clinical trial to promote and place gallic acid and its derivatives on the commercial market.

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