Ameliorative effect of gallic acid in paclitaxel-induced neuropathic pain in mice

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1. Introduction

Paclitaxel (PT) is a potent cancer chemotherapeutic agent and it is used widely for the management of various cancers i.e., breast, lung and ovarian cancer. Clinically, PT is indicated to the management of multiple cancer disorders [1]. Unfortunately, it causes neurodegeneration of a peripheral nerve ending, leading to progress the painful neuropathy [2]. The primary toxic mechanism of PT has altered the production of microtubulin polymerization via synthesis of free radicals, TNF-α, and BCL2 proteins; alteration of cellular pro & anti-oxidant enzymes; calcium dyshomeostasis; and the opening of mitochondrial permeability transition pores (MPTP) [3–5]. Experimentally, administration of PT documented to produce the neuropathic pain symptoms in rodents as well as in humans [6,7]. However, the avoidance of PT prescription is challenging because it has higher efficacy, potency, improvement of the quality of life and affordable price (cheaper) for cancer patients [8]. Therefore, the management of PT associated neurodegenerative process and neuropathic pain symptoms are an emerging field in neurological research.

Neuropathic pain is not a symptom; it is a disease itself. Neurodegeneration of the central and peripheral nervous system causes neuropathic pain. An indication of neuropathic pains is unpleasant, painful sensation and/or lack of sensation [9]. Management of neuropathic pain disorder is very complicated due to multiple complex mechanisms, and available conventional drugs produce only symptomatic relief of neuropathic pain. The most recommended medicines for neuropathic pain are narcotic i.e., morphine and codeine; anti-depressants i.e., desipramine and imipramine; and anti-epileptic drugs like carbamazepine, gabapentin, and phenytoin [10,11]. Paradoxically, these agents have shown less satisfactory action on neuropathic pain and also produce potential toxic effects [12–14]. Therefore, the identification of safer alternatives is urgently needed for the mitigation of painful neuropathy. Various reports have suggested that natural products like herbal and nutritional plants play a key role in the management of neuropathic pain during chemotherapeutic treatment [5].

The present study has been investigated the role of gallic acid (GA) in paclitaxel-induced neuropathic pain. The neuropathic pain was developed with paclitaxel (PT: 2 mg/kg, i.p.) administration in mice. GA (20 and 40 mg/kg) and pregabalin (PreG: 5 mg/kg) were administered intravenously for 10 consecutive days. The neuralgic sensations were investigated by assessing various pain tests like acetone drop, pinprick, plantar, tail flick, and tail pinch test. Mice pain behaviors were evaluated on 0, 4th, 8th, 12th and 16th days. The levels of sciatic nerve thiobarbituric acid reactive substances (TBARS), reduced glutathione (GSH), superoxide anion, calcium, myeloperoxidase (MPO), and TNF-α were estimated. Treatment of GA and PreG attenuate PT induced thermal & mechanical hyperalgesia and allodynia symptoms along with the reduction of TBARS, total calcium, TNF-α, superoxide anion, and MPO activity levels; and decreased GSH level. Therefore, it has been concluded that GA has potential neuroprotective actions against PT induced neuropathic pain due to it’s anti-oxidant, anti-inflammation and regulation of intracellular calcium ion concentration.
neuropathic pain and wellness of neurological functions \[15,16\]. The primary benefits of these molecules are the lack of adverse effects with chronic use and attractive cost-effect relationships.

Moreover, some of the plant extracts of Acorus calamus, Ocimum sanctum, Butea monosperma, Citrullus colocynthis, Ginkgo biloba, Curcuma longa, Mitragyna speciosa, Phyllanthus amarus and Salvia officinalis prevent neuropathic pain \[17\]. In addition, phytoconstituents e.g., celestrol \[18\], liquiritigenin \[19\], tocotrienol \[20\], lycopene \[21\], thymoquinone \[22\], epigallocatechin gallate \[23\] and resveratrol \[24\] also produce anti-neuralgic action. Gallic acid (GA) is a polyphenolic secondary metabolite of various plants \[25,26\]. GA also produces anti-oxidant action in a biological system \[27\]. In addition, plant-derived natural products are capable to produce the cytotoxic (cancer cell) \[28\], and chemo-preventive actions \[29\].

GA is a primary anti-oxidant component of tea extract. Ayurvedic herbs have large quantities of GA \[26,30,31\]. Experimentally, GA has been documented to produce anti-hyperlipidemic, cardioprotective, anti-diabetic activity \[32,33\]. Furthermore, GA has potential neuroprotective action due to mono and poly-targeted actions \[34,35\]. In addition, an acute and sub-acute toxicity study of GA (5000 mg/kg; per oral) documented that, GA did not produce any serious adverse effects and organ toxicity \[36\]. Therefore, GA may be recommended for use in chronic neurodegenerative disorders due to its higher safety margin. However, the experimental evidence of GA in neuropathic pain disorder is limited. Earlier, pregabalin (PreG) is widely employed to manage the seizure attacks; nowadays, it used for the management of diabetic and postherpetic neuropathic pain \[37\]. The exact molecular mechanism of PreG has not been fully explored. However, it is reported to act via reduction of presynaptic neurotransmitter release, like substance P and glutamate, via neuronal N-type calcium channel blocking action \[37,38\]. Experimentally, PreG produces potent neuropathic pain relieving action. Hence, PreG was used as a reference control in this study. Based on this review of the literature, the present study has been investigated the therapeutic role of GA in PT induced neuropathic pain in mice.

2. Materials and methods

2.1. Animals

About 20–25 g weight, age of 10-month-old and disease free male Swiss albino mice were used for evaluation of GA in PT induced neuropathic pain. Animals were kept at standard laboratory diet, temperature (65–75 F; 18-23 °C) and humidity (40–60 %) condition. All animals were kept one week in laboratory condition for acclimatization with 12 h light-dark cycle. The mice were allowed to take the rodent diet and water spontaneously (ad libitum). The experimental design was accepted by the Institutional Animal Ethics Committee (IAEC) to carry out this experimental design. IAEC approval No is ATRC/09/14. The care of mice was taken as per IAEC and Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA; Ministry of Environment and Forest, Government of India) guidelines.

2.2. Drugs and chemicals

Sigma Aldrich (Mumbai, India) company was supplied thiobarbaric acid (TBA) and nitro-blue tetrazolium (NBT). The N-naphthylthelylenediamine; sulfanilamide; 1,1,3,3-tetramethoxy propane and GA chemicals were supplied by Sisco Research Laboratories, Mumbai. The rat specific TNF-alpha ELISA kit was procured for TNF-alpha estimation from RayBio, Inc., USA. The rest of the chemical were purchased with an analytical grade from SD Fine Chemicals, Mumbai, India.

2.3. Development of neuropathic pain in mice

The progress of neuropathic pain in mice was achieved by intraperitoneal administration of PT (2 mg/kg; for 5 days) \[6,7,39\]. Nociceptive pain threshold was assessed at different time points like 0, 4th, 8th, 12th and 16th days.

2.4. Experimental protocol

The present study was comprised six experimental groups. Each group comprises eight Swiss albino mice (n = 8). Group I (Control): Mice were not subjected to any drug or vehicle administration. GA and PT were soluable in water. Water is one of the common solvent (or vehicle) and it doesn’t have any pain modulating action. Therefore, a separate vehicle treatment in PT treated animal and vehicle treatment in normal animals not included in this experimental design. Group II (GA per se): Mice received an intravenous dose of GA (40 mg/kg) for 10 days (from day 6) in mice. Group III (PT): PT (2 mg/kg) was administered intraperitoneally for 5 days. Group IV and V (GA; 20 and 40 mg/kg): Mice received an intravenous dose GA (20 and 40 mg/kg) for 10 days from day 6 respectively. The 10 min time intervals were maintained between each administration of GA and PT. Group VI (PreG; 5 mg/kg): Mice received an intravenous dose PreG (5 mg/Kg) for 10 days from day 6. All six groups were involved in the assessment of pain behavior assessment and biochemical estimations. Nociceptive pain threshold was assessed at different time points like 0, 4th, 8th, 12th and 16th days. The end of the study period i.e., 16th day, mice were sacrificed after the assessment of behavioral tests. The samples of the sciatic nerve and surrounding muscular tissues were collected for the estimation of biomarkers levels. Experimental protocol design has been illustrated in Fig. 1.

2.5. Behavioral evaluation

2.5.1. Acetone drop test

Thermal (cold) chemical sensitivity was assessed in the right hind paw by the application of acetone drop as per Choi et al. method \[40\]. Clinically, it similar to chemical (thermal) allodynic symptoms. Briefly, mice were placed in a closed rectangle wire mesh chamber and about 100 μl of acetone was sprinkled on the plantar surface of the right hind paw. The one-minute duration was allowed to observe the chemical cold sensations. This cold sensation was scored as score 1 for paw licking response; score 2 for shaking response; score 3 for lifting duration of the right hind paw within 4 s; score 4 for lifting duration of right hind paw between 5–8 seconds; and score 5 for lifting duration of right hind paw above 8. A total score i.e., 15 were considered as noted as severe neuronal injury. And, the lowest score was considered as neuroprotection.

2.5.2. Pin prick test

The mechanical pain sensation of mice was evaluated as described by Erichsen and Blackburn-Munro \[41\]. Clinically, it resembles pinpoint mechanical hyperalgesic symptoms. The blunted needle was applied (touch sensation) perpendicularly to the right hind paw plantar (mid) surface. The intensity was generated from the detection of brisk withdrawal reaction of the right hind paw. The interval of needle application was maintained six times per minute. The brisk withdrawal of the hind limb was indicated as a painful response. The stimuli were applied in the mid-plantar surface only six times per minutes to avoid the unwanted tissue injury and developments of the wind-up phenomenon.

2.5.3. Plantar test

Mice were engaged to receive the radiant heat stimuli in the right hind paw as described by Hargreaves et al. \[42\]. Clinically, it resembles thermal hyperalgesic symptoms. The right hind paw was located on the slit of the plantar device. Brisk withdrawal of the right hind limb was noted as a thermal hyperalgesic response. Cut-off time i.e., 20 s was maintained to avoid potential tissue damage.
2.5.4. Tail flick test

The thermal (radiant heat) sensation of mice tail part was assessed by observation of tail flick response as per D’Aemour and Smith method [43] with minor changes of Hargreaves et al. [42]. Clinically, it resembles central sensations. The one-centimeter distance from the tail terminal region was located on the slit of the plantar device. Thermal sensitivity of mice tail was noted as tail withdrawal latency. Brisk withdrawal of tail from the plantar device was considered as a progression of neuropathic pain. Cut off stimuli i.e., 15 s was maintained to avoid potential tissue damage.

2.5.5. Tail pinch test

The mechanical pain sensation of mice tail was assessed by observation of tail clamp dislodgment attempts of mice as per Takagi et al. method [44] with minor changes of Moon et al. [45] and Deshmukh et al. [46]. Clinically, it similar to mechanical compression type of pain sensation. Hoffmann clamp was applied near the base of the mice tail and screw was adjusted to make the mechanical compression type of pain within 5 s. An increasing of dislodgment attempts on Hoffmann clamp was noted as a progression of neuropathic pain. Cut-off time i.e., 10 s was maintained to avoid potential tissue damage.

2.6. Biochemical estimation

The isolated tissue samples were maintained in the humidity chamber at 85 percentage of relative humidity. The sciatic nerve homogenate (10% w/v) was prepared with 0.1 M Tris – HCl buffer (pH 7.4); deionised water; and phosphate buffer (pH 7.4) for total protein, thiobarbituric acid reactive substances (TBARS) & reduced glutathione (GSH); total calcium; and tumor necrosis factor-alpha (TNF-α) estimation respectively. Superoxide anion and myeloperoxidase (MPO) activity were estimated from a muscular tissue sample.

2.6.1. Quantification of thiobarbituric acid reactive substances (TBARS)

TBARS was quantified as described by Ohkawa et al. [47]. Absorbance was recorded by a spectrophotometer (UV-1800 UV-vis spectrophotometer, SHIMADZU Corporation, Tokyo, Japan). The wavelength was fixed with 535 nm for estimation of TBARS. A standard plot was made with reference molecules i.e., 1–10 nanomole (nM) of 1, 1, 3, 3-tetramethoxy propane. The results of tissue TBARS levels were indicated as nM of malondialdehyde (MDA) per milligram (mg) of protein.

2.6.2. Quantification of reduced glutathione (GSH)

GSH level was quantified as described by Beutler et al. [48]. Absorbance was recorded by a spectrophotometer at 412 nm wavelength. A standard plot was made with reference molecules i.e., 10–100 microgram (μg) of GSH. The results of tissue GSH levels were indicated as microgram (μg) of GSH per milligram (mg) of protein.

2.6.3. Quantification of total calcium

Total calcium level was quantified as a described method of Severnghaus and Ferrebee [49] with minor changes of Muthuraman et al. [50]. Absorbance was recorded by a spectrophotometer at 556 nm wavelength. A standard plot was made with reference molecules i.e., 100–1000 parts per million (ppm) of calcium chloride. Results of total calcium were expressed as ppm per milligram (mg) of sciatic nerve tissue.

2.6.4. Quantification of tumor necrosis factor-alpha (TNF-α)

The TNF-α level was quantified in sciatic nerve homogenate as described by Muthuraman et al. [51]. Absorbance was recorded by a spectrophotometer at 450 nm wavelength. A standard plot was made with reference molecules i.e., 0–20,000 pg per ml of reference standard i.e., TNF-α kit sample. Results of TNF-α level was indicated as picogram (pg) of TNF-α per milligram (mg) of total protein.

2.6.5. Quantification of superoxide anion generation

Superoxide anion generation level was quantified by Wang et al. method [52] with minor changes of Muthuraman and Singh [53]. Absorbance was recorded by a spectrophotometer at 540 nm wavelength. Results of NBT reduction level was indicated as picomole (pm) per minute per milligram (mg) of the sciatic nerve.

2.6.6. Quantification of myeloperoxidase (MPO) activity

Myeloperoxidase activity level was quantified by a method of Patriarca et al. [54] with a minor change of Grisham et al. method [55]. Absorbance was recorded by a spectrophotometer at 460 nm wavelength. Results of MPO activity level was indicated as units per milligram (mg) of protein per minute.

Fig. 1. Experimental protocol and treatment schedules of GA and PT. Abbreviation: GA, gallic acid, PT, paclitaxel; and PreG, pregabalin.
2.6.7. Quantification of total protein

Total protein level was quantified by a method of Lowry’s et al. [56]. Absorbance was recorded by a spectrophotometer at 750 nm wavelength. A standard plot was made with reference molecules i.e., 1–10 mg of bovine serum albumin. Results of total protein level were indicated as mg per ml of supernatant.

2.7. Statistical analysis

The behavioral and biochemical data were indicated as mean ± standard deviation (SD). Data of pain response tests were analyzed with two-way analysis of variance (ANOVA) via Bonferroni’s post-hoc analysis were applied by utilizing Graph pad prism software (Version-5.0). in addition, tissue biochemical changes i.e., TBARS, GSH, calcium, TNF-α level, superoxide anion, and myeloperoxidase levels were analyzed by utilizing SigmaStatVersion-3.5 software. A probability value i.e., a p-value less than 0.05 was considered statistically significant.

3. Results

3.1. Role of GA in an acetone drop test

The intraperitoneal administration of PT (2 mg/kg) resulted in significant (p < 0.05) rise thermal alldynic sensation as an indication of increasing the scoring of chemical sensation dissimilarity to the control group. Administration of GA (20 and 40 mg/kg, i.v.) attenuated PT induced increase in the scoring of chemical sensation with concentration-dependent manner. Effect of GA is comparable and similar to the PreG treatment group. However, GA (40 mg/kg; i.v.) per se treated group did not show any significant (p < 0.05) changes in PT induced thermal allodynia (Fig. 2).

3.2. Role of GA in the pinprick test

The intraperitoneal administration of PT (2 mg/kg) resulted in significant (p < 0.05) rise mechanical hyperalgesic sensation as an indication of an increase in the percentage paw withdrawal level when compared to control group. Administration of GA (20 and 40 mg/kg, i.v.) attenuated PT induced increase in the paw withdrawal response with concentration-dependent manner. Effect of GA is comparable and similar to the PreG treatment group. However, GA (40 mg/kg; i.v.) per se treated group did not show any significant (p < 0.05) changes in PT induced mechanical hyperalgesia (Fig. 3).

3.3. Role of GA in plantar test

The intraperitoneal administration of PT (2 mg/kg) resulted in significant (p < 0.05) rise thermal hyperalgesic sensation as an indication of a decrease in paw withdrawal threshold dissimilarity to control group. Administration of GA (20 and 40 mg/kg, i.v.) attenuated PT induced a decrease in paw withdrawal threshold with concentration-dependent manner. Effect of GA is comparable and similar to the PreG treatment group. However, GA (40 mg/kg; i.v.) per se treated group did not show any significant (p < 0.05) changes in PT induced thermal hyperalgesia (Fig. 4).

3.4. Role of GA in tail flick test

The intraperitoneal administration of PT (2 mg/kg) resulted in significant (p < 0.05) rise thermal hyperalgesic sensation as an indication of a decrease in tail withdrawal threshold dissimilarity to control group. Administration of GA (20 and 40 mg/kg, i.v.) per se treated group did not show any significant (p < 0.05) changes in PT induced thermal hyperalgesia (Fig. 5).

3.5. Role of GA in tail pinch test

The intraperitoneal administration of PT (2 mg/kg, i.p. for 5 consecutive days) resulted in significant (p < 0.05) rise mechanical hyperalgesia as an indication of an increasing number of dislodgement of the Heffner’s clamp when compared to control group. Administration of GA (20 and 40 mg/kg, i.v.) attenuated PT induced decrease tail withdrawal threshold with concentration-dependent manner. Effect of GA is comparable and similar to the PreG treatment group. However, GA (40 mg/kg; i.v.) per se treated group did not show any significant (p < 0.05) changes in PT induced mechanical hyperalgesia (Fig. 6).

3.6. Role of GA in tissue biomarker changes

The intraperitoneal administration of PT (2 mg/kg) resulted in significant (p < 0.05) rise TBARS, total calcium, TNF-α, superoxide anion

Fig. 2. Role of GA in acetone drop test (paw thermal alldynia). Digits in parenthesis indicate dose in mg/kg. Data were expressed as mean ± SD, n = 6 mice per group. # p < 0.05 when compared to control group. * p < 0.05 when compared to the PT group. Abbreviation: GA, gallic acid, PT, paclitaxel; and PreG, pregabalin.
& MPO levels; and a decrease in GSH content as an indication of oxidative stress, inflammation, and neuronal damage when compared to control group. Administration of GA (20 and 40 mg/kg, i.v.) attenuated PT induced changes of above tissue biomarkers with concentration-dependent manner. Effect of GA is comparable and similar to the PreG treatment group. However, GA (40 mg/kg; i.v.) per se treated group did not show any significant (p < 0.05) changes in PT induced tissue biomarker changes (Tables 1 and 2).

4. Discussion

The present study revealed that the intraperitoneal administration of PT (2 mg/kg) significantly (p < 0.05) produced neuropathic pain by accelerating thermal & mechanical hyperalgesia and allodynia in paw and tail regions. It indicates that PTTs enhancing neuronal excitation and accelerating neuropathic pain impulses [57]. Moreover, PT treatment also raises the sciatic nerve TBARS, total calcium, TNF-α, NBT reduction, and MPO activity levels along with the reduction of reduced glutathione levels. Results indicate that PT induces neuronal biomarkers mediated neuropathic pain like activation free radical generation, lipid peroxidation, calcium dyshomeostasis, raise inflammatory mediators and neuroinflammation. The treatments of GA (20 and 40 mg/kg, i.v.) attenuated the PT induced pain behavior and biochemical changes. It indicates that GA possesses the natural potency for prevention of neuronal firing, neurodegeneration, and neuroinflammation.

PT associated progression of painful neuropathy is a widely used model for testing of chemotherapy-induced polyneuritis type of neuropathic pain [58]. The relevance of humans pathology is similar to that of complex regional pain syndrome (CRPS) [59,60]. PT causes neuroinflammation and neurodegeneration via accumulation of intracellular calcium (Ca^{2+}) ion concentrations [61–62,63,64], release of inflammatory cytokines [11], and alteration of neuronal microtubulin & myelin proteins [65,66]. In addition, PT also alters the neurovascular system leading to enhance the neuropathic pain symptoms [67]. Our recent findings revealed that alteration of a neuronal microvascular
system is primary cardinal signs for the damage and degeneration of the nervous system [68–70]. Furthermore, some of our studies and other laboratory reports recommended that plant extracts and nutritional products of *Acorus calamus* [51,70], *Butea monosperma* [71], *Swietenia mahagoni* [72], *Ocimum sanctum* [73] and *Vernonia cinerea* [74] mitigate neuropathic pain symptoms. Phytoconstituents like puerarin [75], bulleyaconitine A [76], thymoquinone, epigallocatechin gallate, lycopene and resveratrol [17] produced an anti-neuralgic effect. Experimentally, GA has shown inhibition of histamine release, free radical scavenging action; reduction of oxidative stress, neuroinflammation and cytokine production [77,78,79]. Furthermore, the modern treatment approaches i.e., plant-derived medicines and genetic therapies are contributing to the amelioration of neuroinflammation and neurodegeneration [80]. Present results also indicate GA attenuates PT induced neuropathic pain symptoms via reduction TBARS, tissue total calcium, TNF-α, superoxide anion, MPO levels and prevents the reduction of GSH level.

PT enhances neuronal free radical production. Abundant accumulation of cytosolic free radicals is known to activate lipid peroxidation of the neuronal membrane [33]. In the present study, lipid peroxidation products (TBARS) levels were estimated by a spectrophotometric method [47]. Recent methods like high-performance liquid chromatography, enzyme-linked immunosorbent assay, gas chromatography, and fluorescence are also used for the quantification of TBARS levels [81]. However, this method is very common and widely employed for the assessment of cell membrane lipid peroxidation levels [82]. Subsequent reaction of lipid peroxidation is also altered cellular endogenous antioxidant substances i.e., GSH in PT treated animals. Same results were obtained in this research work and other research laboratory research reports [83]. Thereafter, neuronal structure, receptor expression (up-
Abbreviation: GA, gallic acid, PT, paclitaxel; PreG, pregabalin; TBARS, thiobarbituric acid reactive substances; and GSH, reduced glutathione.

Digits in parenthesis indicate dose in mg/kg. Data were expressed as mean ± SD, n = 6 mice per group. *p < 0.05 vs control group, †p < 0.05 vs PT control group. Abbreviation: GA, gallic acid, PT, paclitaxel; PreG, pregabalin; NBT, nitroblue tetrazolium; and MPO, myeloperoxidase.

down regulation) and neuronal ion channels proteins are altered leading to enhance resting membrane potential via ionic imbalance [57]. Major secondary messengers of cell signal i.e., calcium accumulation leads to enhance the mitochondrial-mediated neuroinflammation and neurodegeneration [84]. Moreover, neurodegeneration also occurs with the free radical associated acceleration of inflammatory and immunological reactions. PT induced inflammatory and immunological reactions are due to the accumulation of TNF-α and MPO levels [85,86]. The treatment of GA has ameliorative effects against PT induced biomarker changes. From data in hand and literature reports, it is concluded that GA possesses potential ameliorating effect against PT induced neuropathic pain symptoms viz free radical scavenging, reduction of inflammatory cytokines and cytosolic calcium ion concentration. 

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Transparency document

The Transparency document associated with this article can be found in the online version.

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