

Research Article

Electrochemical Investigations of dopamine by gallic acid isolated from *Pterocarpus marsupium* Roxb carbon paste electrode : A voltammetric study

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Gallic acid was isolated from the stem bark of *Pterocarpus marsupium* Roxb and the obtained compound was used as the modifier to study the electrochemical investigations of dopamine at modified carbon paste electrode *in vitro* by cyclic voltammetric technique. The effect of scan rate and concentration at modified carbon paste electrode shows the overall electrode process was both diffusion and adsorption-controlled. The same modified electrode was used for the detection of dopamine *in vivo* by differential pulse voltammetric technique. This method can also be used for other bioactive molecules.

Keywords : Gallic acid, *Pterocarpus marsupium* Roxb, Carbon Paste Electrode, Dopamine, Cyclic Voltammetry

Pterocarpus marsupium Roxb. (Leguminosae), also known as Indian Kino or Bija Sar, is a large tree common to the mixed deciduous forests of central and peninsular India (Jain *et al.*, 1968). Extracts of the leaves, flowers, and gum of this tree have been used medicinally in the treatment of diarrhea, toothache, fever, and urinary tract and skin infections (Jain *et al.*, 1968, Chopra *et al.*, 1958). A large number of plants are rich sources of gallic acid either in free form or as a part of tannin molecule (Borde *et al.*, 2011). *P.marsupium* being one among them is rich in tannins. Gallic acid is known to have anti-inflammatory, antimutagenic, anticancer and antioxidant activity (Gichner *et al.*, 1987, Huang *et al.*, 1995, Inouc *et al.*, 1995, Kroes *et al.*, 1992, Mandson *et al.*, 1995, Mirvish *et al.*, 1975, Nakatani *et al.*, 1992). It also seems to

have antifungal, antiviral (Mankani *et al.*, 2004) and antibacterial properties (Mankani *et al.*, 2005). Gallic acid was found to show cytotoxicity against cancer cells without harming healthy cells. Gallic acid is used as a remote astringent in cases of internal haemorrhage. It has been found very beneficial in uterine, pulmonary, and nephritic haemorrhages. It has given benefit in purpura (Manickam *et al.*, 1997). It is used to treat albuminuria, diabetes and it is also known as matrix-metalloproteinase inhibitor (Qiabin *et al.*, 2005). All these properties make gallic acid a pharmacologically important compound.

Dopamine is considered as the potent neurotransmitter present in brain. DA affects brain processes that control movement, emotional response, and ability to experience

pleasure and pain. Regulation of dopamine plays a crucial role in our mental and physical health. Neurons containing the neurotransmitter dopamine are clustered in the midbrain in an area called the substantia nigra. In Parkinson's disease, the dopamine-transmitting neurons in this area die. As a result, the brains of people with Parkinson's disease contain almost no dopamine. To aid relieve this symptom, L-DOPA is given, a drug that can be converted in the brain to dopamine. DA, a catecholamine is thought to be essential in the expression of a wide variety of behaviors (Montague *et al.*, 2004, Pezze *et al.*, 2004, Rye, 2004). DA present in the basal ganglia is involved in motor control, and a causative link has been established between loss of DA in the dorsal striatum, due to neurodegeneration, and Parkinson's disease in humans (Gluck *et al.*, 2004). DA regulates cognitive functions in prefrontal cortex (Cools *et al.*, 2004); DA imbalance in this region can lead to attention disorders and has been involved in the pathophysiology of schizophrenia (Leng *et al.*, 2004, Lynel *et al.*, 2004, Palsson *et al.*, 2005, Zhang *et al.*, 1998). Another crucial role for DA has been established in the expression of rewarding behaviors (Garris *et al.*, 1999, Reynolds *et al.*, 2001), such as eating (Antelman *et al.*, 1975, Roitman *et al.*, 1994) and sexual activity (Ahlenius *et al.*, 1987, Mas *et al.*, 1995). Indeed, many of the common drugs of ill-use such as cocaine, amphetamine, and ecstasy (Phillips *et al.*, 2003, Ferguson *et al.*, 2003, Sprague *et al.* 1998, Parkin *et al.*, 2003) have specific actions on brain DA systems, and this process may be related in the addictive properties of these agents. A number of procedures have been developed, which includes sampling, spectroscopic and electrochemical methods (Bungay *et al.*, 2003, Crespi *et al.*, 2004, Phillips *et al.*, 2003, Burmeister *et al.*, 2003, O'Neill *et al.*, 2003), to study neurochemical phenomena in the indiscrete brain. One such

group of approaches focuses on the in place detection of substances in brain extracellular fluid (ECF), using *in-vivo* voltammetry (IVV) with implanted carbon paste electrodes. This paper explains the application of one approach to the use of ironically employed carbon paste electrodes (CPEs) that are reliable enough to detect a metabolite of DA progressively over periods of time (O'Neill, 2005).

Materials and methods

Dopamine hydrochloride (DA) was purchased from Himedia and stock solution of 25×10^{-4} M was prepared in 0.1M perchloric acid solution, Urethane was obtained from Sigma-Aldrich, graphite powder, silicone oil. All other chemicals were of analytical grades. Acetate buffer solutions (ABS 0.2M) was prepared by mixing standard stock solutions of 0.2 M CH_3COOH and 0.2 M CH_3COONa and adjusting the pH with 0.2 M NaOH. A freshly prepared solution of DA was used in all experiments. All the solutions were prepared with double distilled water.

The cyclic voltammetric and differential pulse voltammetric measurements were performed on the model CH660c (CH instrument). All electrochemical experiments were performed using three electrode single component cell system containing bare carbon paste electrode (BCPE) and modified carbon paste electrode (MCPE) as the working electrodes. Aqueous saturated calomel electrode and platinum as reference and counter electrodes for the electrochemical experiments.

The stem bark of *P.marsupium* was collected from Shimoga district. The shade dried material was cut into fine pieces and powdered by a mechanical grinder and stored in air tight containers until used. This was later subjected to sequential distillation with solvents petroleum ether, chloroform and ethanol by soxhlet extraction method, which was then filtered. The filtrates were

concentrated and vacuumed. The ethanol extract was used for further studies and was labeled PME.

Phenolic acids present in PME was analyzed by HPLC (Model LC-10ATVP), Shimadzu Corporation, Kyoto, Japan) on a reversed-phase Shimpak C18 column (5 μ m, 250mm \times 4.6mm). Phenolic content in the extracts were detected using octadecylsilyl-silica gel as stationary phase. Solvent system consisting of [A] phosphoric acid : water

(0.5:99.5, v/v) and [B] acetonitrile was used as mobile phase at a flow rate of 1mL min⁻¹. Phenolic acid standards such as gallic acid, ellagic acid, p-coumaric acid, hydrobenzoic acid vanillic acids were employed for identification of phenolic acids present in ethanol extract of stem bark of *P.marsupim* by comparing the retention time under similar experimental conditions (Fig.1). The detector used to analyze was UV detector at 220nm.

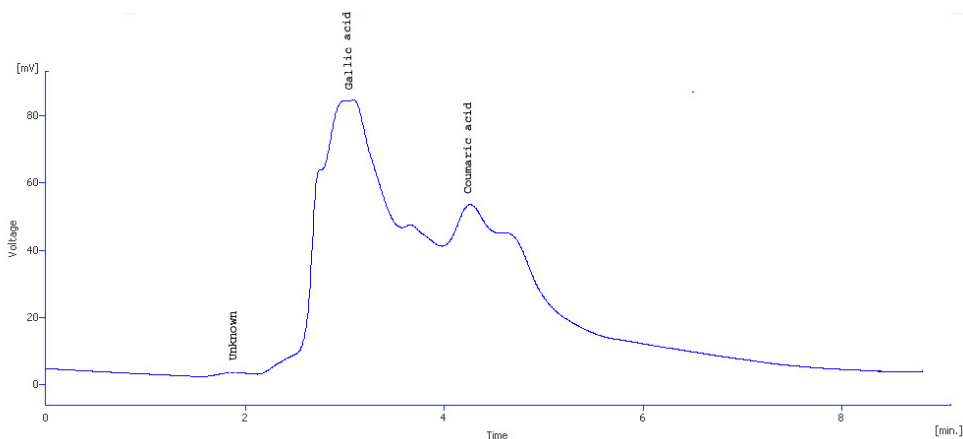


Fig.1 : HPLC of ethanol extract

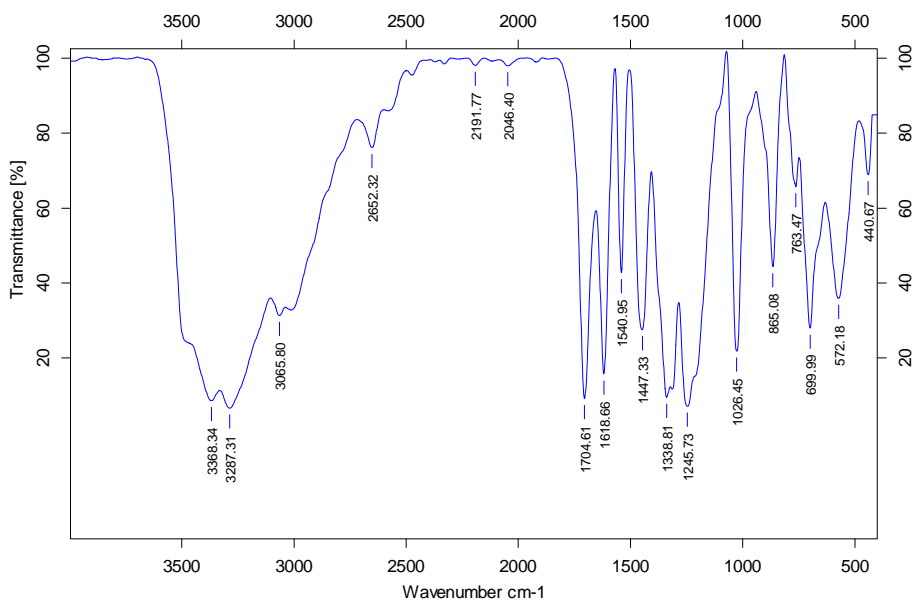


Fig.2.: IR Spectra of isolated compound

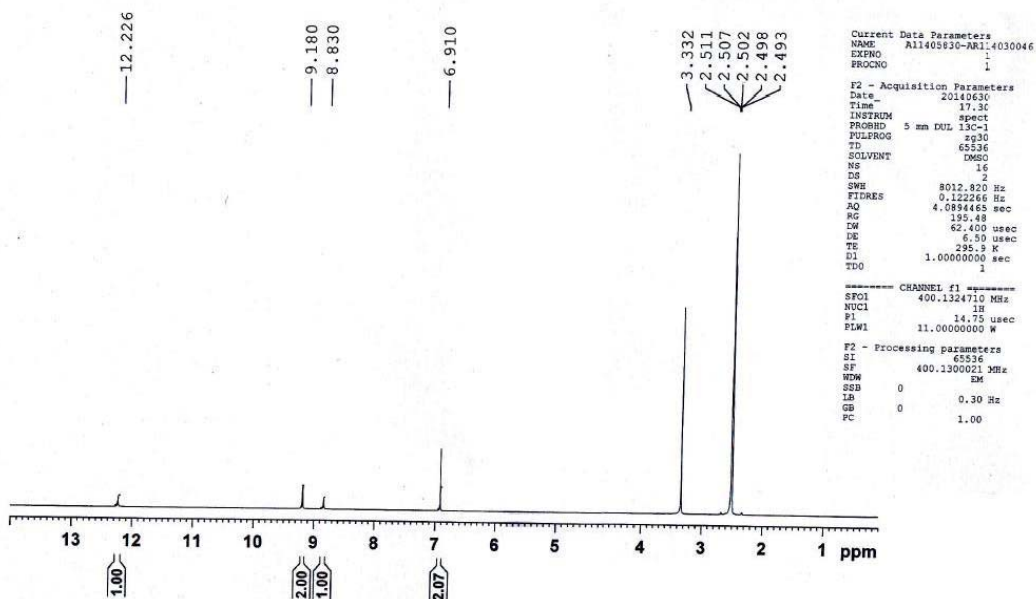


Fig. 3. NMR spectra of isolate compound

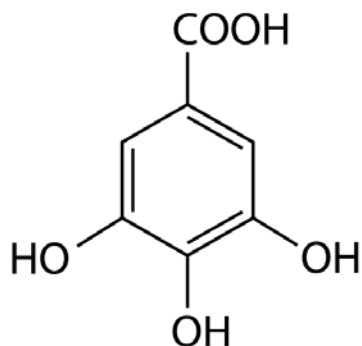


Fig.3a : 3,4,5 trihydroxy benzoic acid (gallic acid)

Isolation of the compound was achieved by column chromatography, in which the PME was eluted through the silica gel and the solvent system being mixture of ethyl acetate-ethanol-water (1:5:4, v/v/v) successively yielded an amorphous compound. The melting point of the isolated compound was found to be 251- 255°C. The qualitative group testing for phenolic acids was found to be positive. To the isolated compound (1 ml of ethanol extract) 10 ml of distilled water was added and filtered. When

Ferric chloride reagent (3drops) was added to the filtrate a green precipitate was formed confirming the presence of gallic acid.

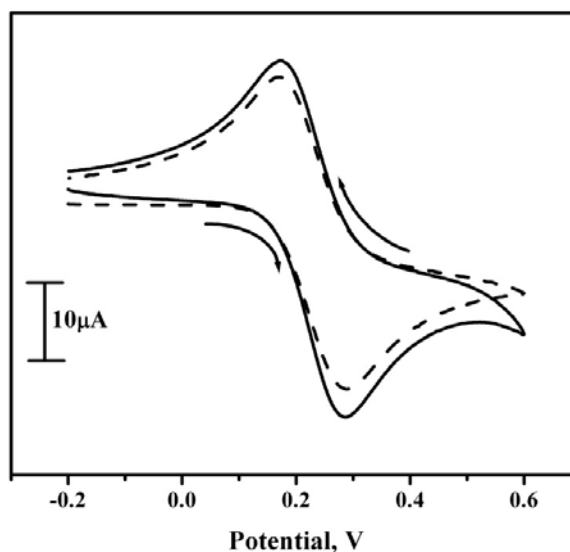


Fig 4a: Cyclic voltammograms of 1 mM potassium ferrocyanide at BCPE (dashed line) and Gallic acid MCPE (solid line) at scan rate of 0.05 Vs⁻¹.

IR spectra: Broad absorption bands between 3287 to 3368 cm^{-1} is due to -OH functional group. Absorption band at 1704 cm^{-1} is due to -C=O- functional group (Fig. 2).

NMR: Singlet at $\delta = 12.22$ is due to -COOH proton, another singlet $\delta = 9.18$ is due to two -OH protons and a singlet at $\delta = 8.83$ due to phenolic -OH. Singlet at $\delta = 6.9$ due to two aromatic protons (Fig.3). Thus the molecular formula of the isolated compound can be deduced as $\text{C}_7\text{H}_6\text{O}_5$ and characterized as 3,4,5 trihydroxy benzoic acid (gallic acid)(Fig.3a).

Preparation of Bare Carbon Paste Electrode

Carbon paste was prepared by grinding the 70% graphite powder of 50mm particle size and 30% silicon oil in an agate mortar by hand mixing for about 30 minute to get homogenous bare CPE. The paste was packed into the cavity of homemade carbon paste electrode of 3mm diameter and smoothed on weighing paper.

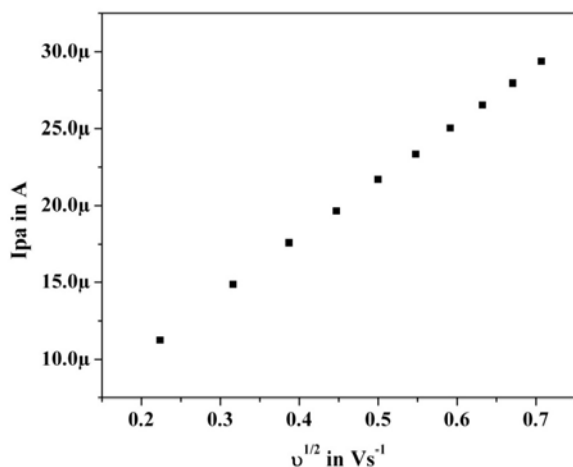


Fig 4b: Graph of anodic peak current vs. square root of scan rate.

Preparation of gallic acid modified carbon paste electrode

Gallic acid modified electrode was prepared by grinding the different ratios of gallic acid

with 70 % graphite powder of 50 mm particle size and 30 % silicon oil in an agate mortar by hand mixing for about 30 minutes to get homogeneous paste. The paste was packed into the cavity of homemade CPE of 3mm in diameter and smoothed on weighing paper.

Statistics : All values are expressed as the mean \pm SEM (standard error of the mean). The data were evaluated by one way analysis of variance (ANOVA) followed by Duncan's test. The differences in values at $P < 0.05$ or $P < 0.01$ were considered as statistically significant. Statistical analysis was performed by Microcal origin 6.0 version.

Results and Discussion

Electrochemical response of $\text{K}_3\text{Fe}(\text{CN})_6$ at gallic acid modified carbon paste electrode

The surface area of CPE was determined by using potassium ferrocyanide system in 1 M KCl. The effect of scan rate on cyclic voltammograms of 1mM solution of ferrocyanide has been studied at 0.05, 0.06, 0.07, 0.08, 0.09, and 0.1 Vs^{-1} . For a reversible redox couple, the number of electrons transferred in the electrode reaction can be determined by the separation between the peak potentials $\Delta E_p (E_{pa} - E_{pc}) / n \sim 0.059$ V. The value found to vary from 0.061 V and 0.065 V which corresponds to one electron transfer. The ratio of i_{pa} / i_{pc} was found to be close to one (0.9953) which is a typical behaviour, exhibited by a reversible electrochemical transfer. On substitution of the diffusion-coefficient value ($12.2 \times 10^{-6} \text{ cm s}^{-1}$) in the following equation (Galus & Adams, 1963, Mahanthesha *et al.*, 2013, Hegde *et al.*, 2008).

$$i_p = (2.69 \times 10^5) n^{3/2} D^{1/2} v^{1/2} C_o$$

where i_p is the peak current, n is the stoichiometric number of electrons involved in the electrode reaction, A is the area of electrode in cm^2 , D_o is the diffusion coefficient of (cm^2s^{-1}), C_o is the concentration

(mol/cm³) and ν is the scan rate in (Vs⁻¹). Based on the above equation the surface area of the electrode was found to be 0.029 cm². The same procedure was followed for gallic acid and it was found to be 0.036 cm².

Owing to the complex properties and the roughness of the electrode surface, the CVs of bare CPE (solid line) and gallic acid modified electrode (dashed line), which were recorded in 1X10⁻³M K₄[Fe(CN)₆] solution containing 1M KCl as supporting electrolyte at a scan rate of 50 mV/s. A well-defined redox peak with significant enhancement was observed at modified CPE when compared with bare CPE. This may be ascribed to the higher electrochemical activity of the modified CPE. Compared with the bare CPE the peak current at modified CPE increased and was three folds of that on bare CPE. Due to increased peak current the modified

electrode possesses the highest electro-catalytic activity (Niranjana *et al.*, 2009, Chitravathi *et al.*, 2009).

Effect of scan rate

The figure 4a shows the cyclic voltammograms of 1X10⁻³M K₄[Fe(CN)₆] on different scan rates. With the increase of scan rate the redox peak currents also increased gradually. The relationship of the anodic peak current with scan rate was constructed and the results are shown in the figure 4b in the range from 50-400mV/s. The anodic peak currents were proportional to the scan rate with correlation coefficient 0.9986, which indicates the electrode process was diffusion - controlled (Reddy *et al.*, 2012, Chandrashekar *et al.*, 2012).

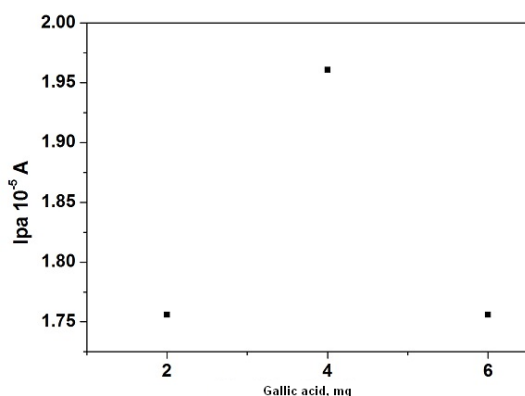


Fig.5: Plot of anodic peak current vs. concentration of gallic acid

Effect of gallic acid on the anodic peak current of DA

Gallic acid MCPE was prepared by adding different amounts of gallic acid to the carbon paste electrode. It was employed for the oxidation of 0.1mM DA in PBS 7.4 using cyclic voltammetric technique. By increasing the quantity of gallic acid in the modification, the electrochemical anodic peak current (I_{pa}) goes on increasing at a particular ratio. The

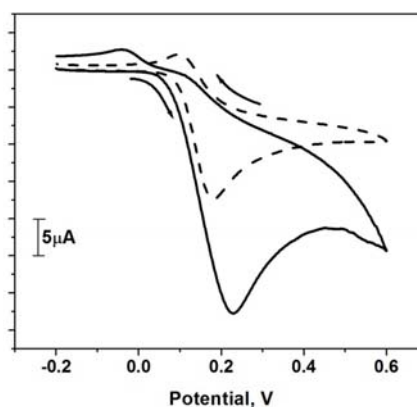


Fig .6 : Cyclic voltammograms of 0.4 mM Dopamine at BCPE (dashed line) and sample-1 MCPE (solid line) at scan rate of 0.05 Vs-1.

modification of gallic acid MCPE from 2mg to 6mg has been calibrated. The redox peak currents were increased up to 4mg gallic acid in carbon paste electrode. After this, further increase in the quantity of gallic acid the redox peak currents were decreased as shown in figure 5. Therefore 4mg gallic acid was chosen as optimum for all further electrochemical studies.

Electrocatalytic oxidation of DA at gallic acid

The figure 6 shows the cyclic voltammograms obtained for the electrochemical response of DA at the modified CPE (solid line) and bare CPE (dashed line) in phosphate buffer solution at pH 7.2. At bare CPE, DA shows the oxidation and reduction peak potentials and under the identical conditions, the modified CPE produces significantly increased peak currents and a more reversible electron process of DA with the lesser oxidation and reduction peak potentials. The enhancement of peak currents provides clear evidence of the catalytic effect of modified CPE. The obtained results of the enhancement of the peak currents showed the excellent catalytic activity (Shankar *et al.*, 2014, Mahanthesha *et al.*, 2014, Sathisha *et al.*, 2014).

Effect of scan rate on the peak currents of dopamine

The figure 7 and 8, shows the anodic peak current of 0.1mM DA on the modified CPE versus scan rate and square root of different scan rates. This was carried out in order to investigate the kinetics of the electrode reactions and verify whether the process is adsorption or diffusion controlled processes. The relationship of the redox peak currents with the scan rate was constructed and the results are shown in figure 8. In the range from 50-400 mVs⁻¹ the redox peak currents were proportional to the scan rate, (γ) which indicates that the electron transfer reaction was adsorption-controlled (Bard *et al.*, 1980, Nicholson & Shain *et al.*, 1964, Adam, 1996). The observation shows that with the increased scan rate, the redox peak currents also increased gradually and the plot of anodic peak current and scan rate shows linearity indicates the process is adsorption controlled. The graph of anodic peak current and the square root of scan rate shows linearity and this confirms diffusion-

controlled. The overall electrode process is controlled by both adsorption and diffusion controlled process at modified carbon paste electrode (Chandrashekar *et al.*, 2011, Sathisha *et al.*, 2014, Mahanthesha *et al.*, 2014).

Effect of concentration of DA

The electrocatalytic oxidation of DA was carried out by varying the concentration of DA at modified CPE. By increasing the concentration of DA, the electrochemical anodic and cathodic peak currents goes on increasing with shifting E_{pa} towards positive and E_{pc} with negligible shifting of 1.0×10^{-4} to 10.0×10^{-4} M DA concentrations. The plot of I_{pa} vs concentration (Fig.5) showed increase in the electrochemical peak current. The graph obtained linearly increased in peak current with increase in the DA concentration (Avendano *et al.*, 2010, Corona *et al.*, 2009, Alarcon *et al.*, 2008).

The concentration of DA was varied from 1.0×10^{-4} to 10.0×10^{-4} M. Figure 11 shows the graph of anodic peak current vs concentration of DA shows two linear relationships ranges 1×10^{-4} M - 3×10^{-4} M and 4×10^{-5} M - 10×10^{-4} M with the linear regression equations as $I_{pa} (\mu A) = 5.891 (C_0 \times 10^{-4} \text{ M/L} + 0.656 (\mu A))$ and $I_{pa} (\mu A) = 1.411(C_0 \times 10^{-4} \text{ M/L} + 13.146 (\mu A))$ respectively. The correlation coefficient for the first linearity was 0.9872 and for the second it was found to be 0.9858. The decrease of sensitivity (slope) in the second linear range is likely to be due to kinetic limitation (Ardakani *et al.*, 2010).

In vivo experiment

To evaluate the use of carbon paste modified electrodes as *in vivo* sensors, we first characterized the electrode response *in vitro* using cyclic voltammetry with gallic acid modified electrode and *in vivo* studies was executed by differential pulse voltammetric technique and the electrochemical response

of dopamine was determined. CPE has continued to offer a variable substrate for analysis, mainly because of the ease with which the surface of this electrode material can be modified with organic, inorganic or biological molecule. For applications

incorporating implantation in biological tissue, carbon paste was prepared by thoroughly mixing graphite powder with silicon oil which could be easily packed into the cavity in the electrode of 3mm diameter and used.

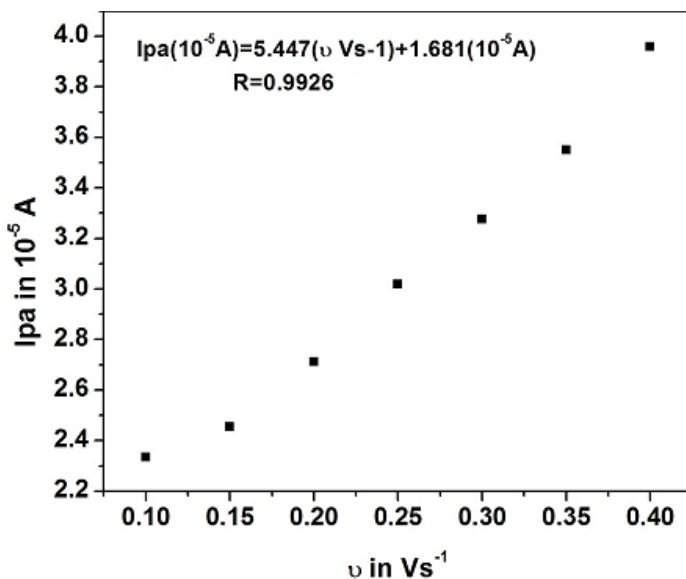


Fig.7 : Graph of anodic peak current Vs Scan rate of DA

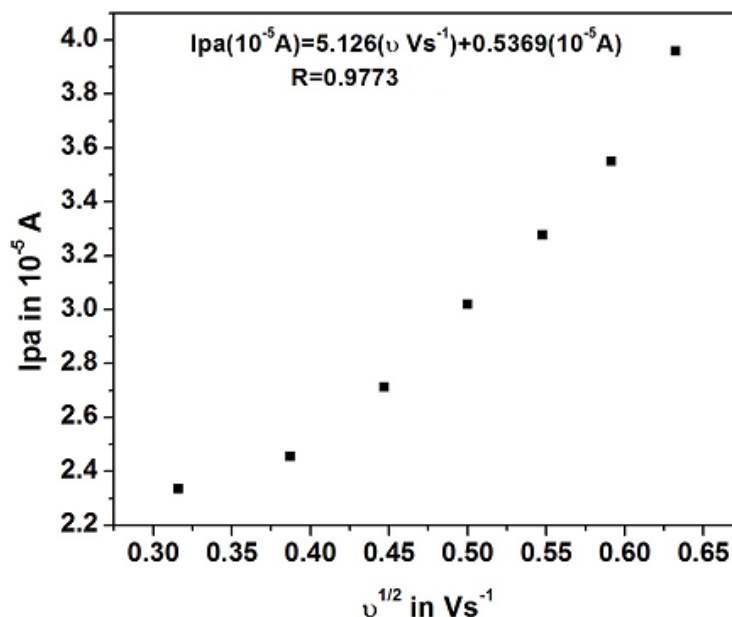


Fig.8 : Graph of anodic peak current Vs square root of scan rate of DA

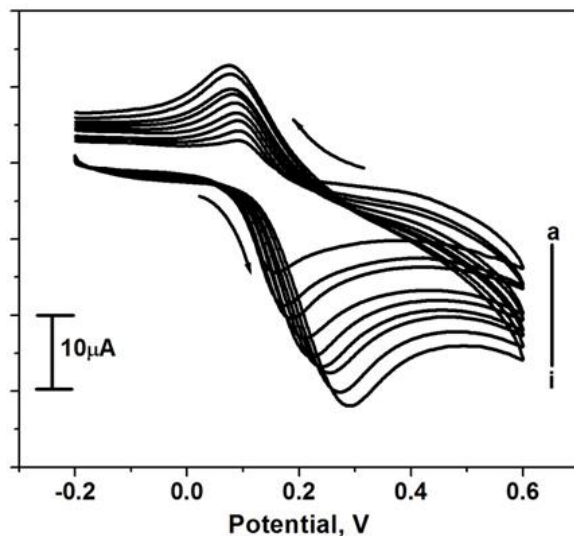


Fig.9 : Cyclic voltammogram of DA in 0.2M PBS solution of pH 7.4 at gallic acid MCPE at scan rate of 0.1Vs^{-1} with different concentration (a-h; $1.0\times 10^{-4}\text{ M}$ to $10.0\times 10^{-4}\text{ M}$)

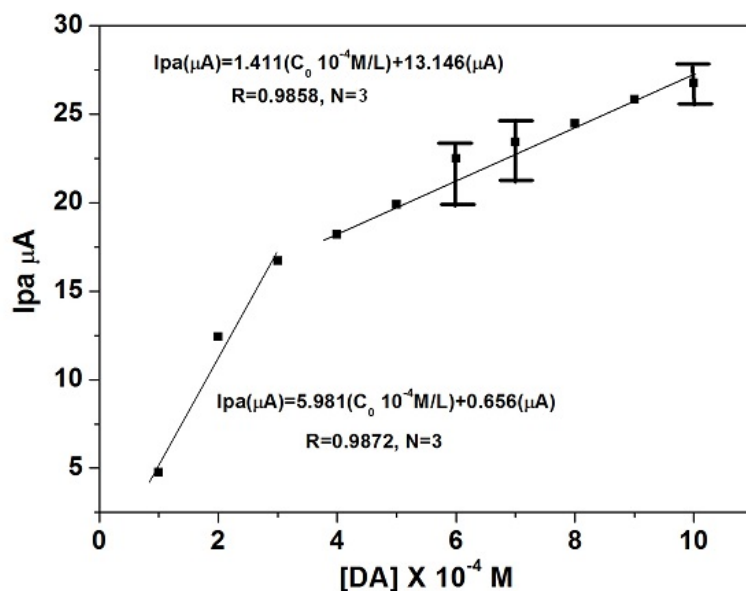


Fig.10 : Graph of anodic peak current Vs concentration of DA

Differential pulse voltammetric technique (DPV) was proposed by Barker and Gardner, (1960). This technique provides greater sensitivity with more efficient resolution and differentiation of various species. This technique differs from normal pulse voltammetry because here each potential pulse is fixed for small amplitude varying

from 0.01 to 0.1s. Current is measured at two points from each pulse, one is just before the application of the pulse and other at the end of the pulse. The difference between the current measurements at these points for each pulse is determined and plotted against the base potential. This method makes a still greater improvement in sensitivity.

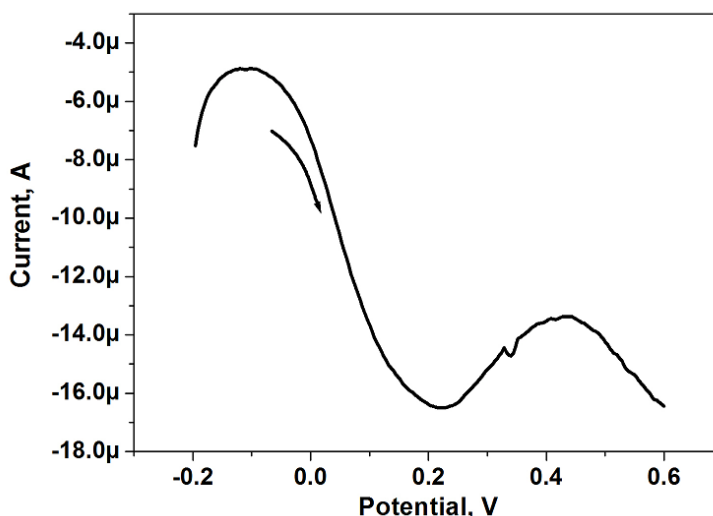


Fig. 11 : Differential pulse voltammogram for modified carbon paste electrode MCPE for dopamine for the rat brain. Scan rate 10 mVs⁻¹; Pulse amplitude 20 mV; Pulse width 60ms; Pulse interval 200ms.

Male Wistar albino rats, weighing about 150 g were used for the study. Animals were housed at (25 ±1)°C and humidity of 55–60%. All animal procedures were approved by the Institutional Ethical Committee (NCP/IAEC/CL/201/01/2012-2013).

Animals were anesthetized with urethane (1.5g/Kg, made in a 50% w/w solution in 0.9% saline). The rat was placed dorsoventrally on the experimental table and the cranium of the brain region was opened for the placement of electrodes. The working electrode (MCPE) was placed on the surface of the brain, Pt and calomel electrodes were placed on either sides of the working electrode in the brain region. The working electrode was adjusted until a robust, stimulated release was obtained which was computer controlled. A single peak was observed in the rat striatum which attributed to the oxidation peak corresponding to dopamine. The differential pulse voltammogram was recorded for the modified carbon paste electrode when the scan rate 10 mVs⁻¹; Pulse amplitude 20 mV; Pulse width 60ms; Pulse interval 200ms was

applied. Peak shaped signal was obtained by non-differential method reasons being both thin layer behavior in the space around the implanted electrode and adsorption of the analyte. A well-defined single peak (Figure 11) was observed which represented the presence of DA, confirming the detection of DA at particular potential; no other interfering electroactive species peaks were shown by the modified electrode for other bioactive molecules which are generally actively present in the animal brain. Therefore the isolated compound gallic acid modified carbon paste electrode acts as biosensor for the electrochemical determination of dopamine.

Conclusions

The result of the present investigation revealed, gallic acid, isolated from the *Pterocarpus marsupium* Roxb when used as a modifier to study the electrochemical response of an interesting neurotransmitter dopamine both under *in vitro* and *in vivo* conditions strongly enhanced both anodic and cathodic peak currents of DA. The

increase in the concentration of DA results in greater enhancement of electrochemical oxidation at certain stage. Electrochemical process was found to be diffusion-controlled. The response was very much similar in both *in vitro* and *in vivo* conditions thus proving that the electrode can sense the presence of the neurotransmitter DA. Therefore the modified electrode shows a good selectivity, sensitivity and reproducibility. With its low cost and ease of preparation, gallic acid modified electrode will have good applications for the further sensor developments in electrochemical sensor field.

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