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Effect of *Plumbago zeylanica* administration on brain neurotransmitter level in Wistar albino rats

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ABSTRACT

According to WHO about 80% of the world's population relies on traditional medicine for their primary health care. *Plumbago zeylanica* L. is a medicinal plant, belong to the family of Plumbaginaceae and the root of *P. zeylanica* contains several bioactive constituent like L-dopa, Plumbagin (naphthoquinone), droseron, chitranone, triterpenoid, anthraquinone. This study is designed to evaluate the effect of *P. zeylanica* and naphthoquinone on the level of various amine neurotransmitters namely epinephrine, norepinephrine, serotonin, 5-hydroxyindole 3-acetic acid (5-HIAA), and dopamine on the discrete regions of the brain tissues. Wistar male albino rats were treated separately with ethanoloic extract of *P. zeylannica* (root) and the commercially purchased phytochemical naphthoquinone at the dose of 2mg/kg b. wt with different experimental groups. The brain tissue homogenates (cerebral cortex, cerebellum, hypothalamus, pons-medulla, midbrain, and corpus striatum) were analyzed to quantify the aforementioned neurotransmitters by high performance liquid chromatography (HPLC). The results showed that, administration of *P. zeylanica* and NQ does not alter the many of the studied neurotransmitter at significant level; however, there is a change in the neurotransmitter profile in few specific regions of Wistar rat brain and striatum was found to be affected more.

INTRODUCTION

Today the scientists of the world are visualizing a great future of plant based drugs for treatment of cancer, AIDS, chronic diseases and viral infections, since plants appear to be an excellent source of new bioactive compounds. Therefore, a worldwide interest is developing rapidly in phytomedicinal sector. *Plumbago zeylanica* L. is a medicinal plant, belong to the family of Plumbaginaceae. *Plumbago zeylanica* (PZ) is an attractive erect rambling shrub with long tuberous root and often occurring as a roadside weed, sometimes cultivated in gardens. PZ is being used for the cure of skin diseases, infections and intestinal worms such as scabies, hookworm dermatitis, acne, ulcers, sores, ringworm and hookworm (Manu pant, 2012). The main constituent in PZ is plumbagin, which forms 50. 27 parts in one gram (De Paiva *et al.,* 2003). Siva Kumar *et al.,* (2005) reported that the plumbagin LD_{50} dose was found to be 16 mg/kg body weight in mice. However, according to Santhakumari and Rathinam (1978), it is 6. 5 mg /kg body weight in albino rats. The Plumbagin, a quinonoid constituent isolated from the root of PZ has been shown to exert anti carcinogenic effect (Srinivas *et al.,* 2004). PZ exhibits an inhibitory effect on carcinogenesis in the intestines, causes cytogenetic and cell cycle changes in mouse and it is also effective in Ehrlich ascites carcinoma, and possesses proliferation activity in human cervical cancer cells (Srinivas *et al.,* 2004). PZisalso reported to have antitumour activity on rat fibrosarcoma (Krishnaswamy and Purushothaman, 1980). Plumbagin, however, showed exceptional antimutagenicity (Edenharder and Tang, 1997). Plumbagin has demonstrated reproductive toxicity in male and female animals. Extracts of the root have been reported to be a powerful poison which, when given internally or applied to the ostium uteri, causes abortion (Premakumari *et al.,* 1977). Krishnaswamy and Purushothaman, (1980) reported that Plumbagin has antimicrobial and antifungal activities.

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Abdul and Ramchender, (1995) also reported that in low doses plumbagin exerted a constant increase in bactericidal activity throughout the study period whereas with a high dose a higher response was observed up to six weeks.

MATERIALS AND METHODS

The chemicals norepinephrine, Epinephrine, 5-hydroxytryptamine (5-HT), 5-hydroxyindole 3-acetic acid (5-HIAA), 3,4, dihydroxy benzyl amine hydrobromide (DHBA) and naphthoquinone were purchased from Sigma. Other chemicals were of analytical grade from Merk (Germany) and SISCO (India).

Animals

Wistar strain male albino rats weighing 180 to 220 g were used for all the animal experiments. Animals were housed in groups of three (rats) per cage and maintained in the animal house. The animals were kept under closely controlled environmental conditions (12-hr light/dark cycle, lights on between 07. 00 and 19. 00 hr, room temperature, 24°C) and allowed free access to food (M/S Hindustan Lever Limited, Bombay, India) and water. The study commenced after obtaining the approval from the Institutional Animal Ethical Committee and Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India. All efforts were made to minimize both the number of animals used and unwanted stress or discomfort to the animals during experimental procedures. All the sample collections were done between 07. 00 and 09. 00AM in order to avoid circadian rhythm induced variation.

Plant and Extraction

The root of the *Plumbago zeylanica* (PZ) was collected locally, identified and authenticated by the Tamil Nadu Medicinal Plant Farms & Herbal Medicine Corporation Ltd. , Chennai, Tamil Nadu - 600 106. The extraction procedure was done according to Bopaiah and Pradhan, (2001). The dried coarsely powdered root of PZ (50g) was extracted with 50% ethanol using a Soxhlet extractor for 24h at constant temperature (50-55°C). Then the extract was concentrated in a water bath under reduced pressure. The semisolid form of the extract was dried in hot air oven. The suspension of the extract was prepared in Olive oil (1:9). Naphthoquinone (NQ) was purchased from Sigma. The ethanolic extract of PZ root as well as the NQ was administered orally by dissolving it in olive oil (1:9) at the dosage of 2mg/kg body weight (Santhakumari and Rathinam, 1978).

Experimental Groups

Experimental animals were divided into 8 groups, each consists 6 animals. Group I animals were control animals (untreated), Group II animals were treated with Olive oil orally. Group III, IV and V animals were treated orally (2mg/kg b. wt) with ethanolic extract of PZ root for 1day, 15days, and 30 days respectively. Group VI, VII and VIII animals were treated NQ (2mg/kg b. wt)orally for 1day, 15days, and 30 days respectively.

Sample preparation

At the end of the experiment, animals were killed by cervical dislocation and the brain was dissected, discrete regions namely cerebral cortex (CC), cerebellum (CB), midbrain (MB), pons-medulla (PM), hippocampus (HP) and hypothalamus (HT) were micro dissected and individual brain regions were homogenized separately using motor driven Teflon-glass tissue homogenizer with 60mg/ml of ice-cold 0. 1 M perchloric acid. Homogenates were centrifuged at 6,000g in a refrigerated centrifuge for 2 min. The supernatant 600 µl was taken in an eppendorf to which dihydroxy benzyl hydrazine (DHBA) 20 µl (200pg) was added as an internal standard. Again, it was centrifuged at 35,000g for 20 minutes. Supernatant was filtered with 0. 22µ membrane filter.

Estimation of brain biogenic amines

The various brain biogenic amines in the discrete regions of the rat brain were estimated by the method of Wagner *et al.*, (1982). Concentrations of Norepinephrine (NE), Epinephrine (E), 5-hydroxytryptamine (5-HT) and 5-hydroxyindole 3-acetic acid (5-HIAA) were measured by high performance liquid chromatography (HPLC) coupled with electrochemical detection as per the method of Kim *et al.*, (1983). Separation and quantization were achieved by reverse phase HPLC column with electrochemical detection.

One mg of NE, E, 5HT and 5-HIAA, were dissolved separately in 10ml of 0. 1M perchloric acid containing 0. 05mM ascorbic acid initially and ran in the HPLC system to determine the retention time of the individual sample. Then all were mixed to make a final concentration to run. No difference in the retention time was observed for the individual neurotransmitter. The mixed solution was stored as stock solution at -70ºC and was freshly prepared once in every two weeks. Just before use, 10µl of each stock solution (containing all the above) was taken and made up to 100ml with distilled water. 20µl from this was injected into HPLC, which contains 200pg of all standards. DHBA was used as internal standards.

Twenty micro liter of sample was injected into a Rheodyne injector (USA) of HPLC system, which was connected to an isocratic pump and reverse phase column for separation of indole amines and catecholamines (Figure 9). The reaction products were detected with electrochemical detector (ECD). The electrochemical detector (ECD) with glassy carbon working electrode was used at a voltage setting of +0. 60 V for monoamines and their metabolites vs. an Ag/AgCl reference electrode. The flow rate was maintained at 0. 8 ml/min. Neurotransmitters were quantified using Shimadzu C-R8A data processor and expressed as nano grams of neurotransmitter per gram of wet weight of brain tissue.

Concentrations of Homovalinic acid (HVA), Dopamine (DA), 3,4, dihydroxy benzyl acetic acid (DOPAC) were measured by HPLC coupled with electrochemical detection as per the system specification above.

RESULTS

Epinephrine (E)

The epinephrine from various groups is summarized in table no-1as mean ± SEM**.** One-day treatment with PZ or NQ didn't alter the epinephrine level all in the brain regions studied. After 15 days treatment PZ did not alter the epinephrine level in any of the regions whereas NQ treatment increased the epinephrine level only in striatum (F = 5, df 7, 40). However, the rest of the regions remain unaffected. The 30 days of PZ and NQ treatment none of the region showed variation. At this dosage, PZ even after repeated exposure did not interfere with the epinephrine.

Norepinephrine (NE)

The norepinephrine from various groups is summarized in table no. 2 as mean ± SEM**.** One-day treatment with PZ or NQ didn't alter the norepinephrine level in the brain. After 15 days treatment with both PZ and NQ treatment increased the norepinephrine level in striatum (F = 9.2, df 7, 40). However, the rest of the regions remain unaffected. The 30 days of PZ and NQ treatment none of the region showed variation. At this dosage, PZ even after repeated exposure did not interfere with the norepinephrine.

Serotonin (5 HT)

The Serotonin from various groups is summarized in **table no - 3**as mean ± SEM. One-day treatment with PZ or NQ didn't alter the serotonin level all in the brain regions studied. After 15 days treatment with PZ didn't alter the serotonin level in all the regions studied. , whereas with NQ treatment showed increased serotonin level in cerebellum (F = 5.6, df 7, 40). However, the rest of the regions remain unaffected. The 30 days of PZ and NQ treatment increased the serotonin level in striatum (F = 7.7, df 7, 40). However, the rest of the regions remain unaffected. At this dosage, PZ even after repeated exposure did not interfere with the serotonin.

5-Hydroxy Indole Acetic acid

The 5 HIAA from various groups is summarized in table no-4as mean ± SEM**.** Irrespective of the duration PZ or NQ administration, the levels of the 5 HIAA did not show any variation from controls indicating (one day, 15 days and 30 days) both of them are not interfering with the normal functions of brain.

Table 1: Effect of PZ and NQ treatment on epinephrine level in brain tissue.

	EPINEPHRINE (ng/g of wet tissue)							
	CONTROL	**VEHICLE**	**PZ 1**	**PZ 15**	**PZ 30**	**NQ 1**	**NQ 15**	**NQ 30**
CC	125 ±3	121 ±5	108 ±5	117 ±5	125 ±5	109 ±8	114 ±7	118 ±3
CB	1460 ± 77	1397 ± 53	1307 ±63	1305 ±33	1394 ±97	1415 ±68	1433 ±76	1367 ±92
HY	1864 ±95	1486 ±51	1421 ±116	1692 ±106	1663 ±104	1596 ±93	1581 ±77	1775 ±133
HP	5774 ±520	5266 ±497	5592 ±323	5658 ±580	6049 ±369	5399 ±432	5424 ±307	5576 ±345
PM	5824 ±318	5437 ±159	6096 ±346	5398 ±349	4920 ±348	5238 ±256	5613 ±490	5487 ±359
ST	2056 ±92	1889 ±110	1982 ±98	2274 ±33	2019 ±36	1934 ±137	2522 ±60 *	2094 ±107

Values are expressed as Mean ± SEM. The '*' represent statistical significance compared with control at p<0. 05. CC: Cerebral cortex, CB: Cerebellum, HY: Hypothalamus, HP: Hippocampus, PM: Pons-Medulla, ST: Striatum. PZ 1, PZ 15, and PZ30 means treatment with *Plumbago zeylanica* for 1 day, 15 days and 30 days respectively. NQ 1, NQ 15 and NQ 30 means treatment with naphthoquinone respectively for 1 day, 15 days and 30 days.

Table 2: Effect of PZ and NQ treatment on nor-epinephrine level in brain tissue.

	NOREPINEPHRINE (ng/g of wet tissue)							
	CONTROL	**VEHICLE**	**PZ 1**	**PZ 15**	**PZ 30**	**NQ 1**	**NQ 15**	**NQ 30**
CC	777 ± 39	654 ±36	711 ±36	668 ± 47	676 ±25	759 ±50	732 ±37	796 ±44
CB	1862 ±125	157 ±106	1836 ±148	1790 ±91	1655 ±117	1679 ±76	1761 ±102	1854 ±100
HY	25165 ± 1206	23016 ± 1280	26078 ± 1049	240613 ± 980	22665 ±823	24801 ±1655	24996 ±1601	24265 ±1140
HP	7817 ± 455	6529 ±520	7778 ±312	7757 ±468	7817 ± 455	7554 ± 422	6301 ±2726	6671 ±602
PM	4200 ±339	4390 ±344	4123 ±263	4687 ±388	3919 ±223	4495 ±322	4707 ±305	4509 ± 242
ST	9482 ±468	9376 ±569	9817 ±278	13872 ±781 *	10200 ±592	10207 ± 580	12550 ± 546 *	9577 ± 407

Values are expressed as Mean ± SEM. The '*' represent statistical significance compared with control at p<0. 05. CC: Cerebral cortex, CB: Cerebellum, HY: Hypothalamus, HP: Hippocampus, PM: Pons-Medulla, ST: Striatum. PZ 1, PZ 15, and PZ30 means treatment with *Plumbago zeylanica* for 1 day, 15 days and 30 days respectively. NQ 1, NQ 15 and NQ 30 means treatment with naphthoquinone respectively for 1 day, 15 days and 30 days.

Table 3: Effect of PZ and NQ treatment on serotonin level in brain tissue.

	SEROTONIN (ng/g of wet tissue)							
	CONTROL	**VEHICLE**	**PZ 1**	**PZ 15**	**PZ 3**	**NQ 1**	**NQ 15**	**NQ 30**
CC	783 ±30	793 ±44	683 ±31	822 ±37	735 ±47	805 ±36	825 ±38	758 ±42
CB	893 ±39	929 ±34	794 ±35	822 ±33	762 ±34	730 ±33	1022 ±42 *	791 ±39
HY	8954 ±440	9228 ±427	9362 ±445	9284 ±415	9876 ±489	9848 ±477	9340 ±469	9225 ±421
HP	4045 ±196	4057 ±207	4212 ±199	3977 ±200	3974 ±157	3930 ±203	3756 ±202	3941 ±146
PM	2646 ±212	2235 ±186	2944 ±207	2901 ±151	2617 ±190	3356 ±174	2948 ±231	3049 ±229
ST	5550 ±140	5078 ±409	5597 ±254	5797 ±200	7400 ±299 *	5112 ±382	5192 ±294	7297 ±289 *

Values are expressed as Mean ± SEM. The '*' represent statistical significance compared with control at p<0. 05. CC: Cerebral cortex, CB: Cerebellum, HY: Hypothalamus, HP: Hippocampus, PM: Pons-Medulla, ST: Striatum. PZ 1, PZ 15, and PZ30 means treatment with *Plumbago zeylanica* for 1 day, 15 days and 30 days respectively. NQ 1, NQ 15 and NQ 30 means treatment with naphthoquinone respectively for 1 day, 15 days and 30 days.

Table 4: Effect of PZ and NQ treatment on serotonin level in brain tissue.

5-HIAA	5-HYDROXY INDOLE ACETIC ACID (ng/g of wet tissue)							
	CONTROL	VEHICLE	PZ 1	PZ 15	PZ 30	NQ 1	NQ 15	NQ 30
CC	63±4	55±2	65±3	55±2	60±3	65±2	64±3	63±2
CB	141±12	156±11	158±11	148±10	125±6	131±12	136±9	143±9
HY	986±84	903±68	1025±90	1048±95	987±55	1021±51	1039±73	1042±67
HP	345±27	321±22	306±17	369±21	429±21	338±25	351±25	391±24
PM	389±30	347±28	353±20	398±33	418±27	372±22	439±30	396±18
ST	826±39	822±31	859±50	824±48	776±53	895±61	814±49	753±50

Values are expressed as Mean ± SEM. The '*' represent statistical significance compared with control at p<0. 05. CC: Cerebral cortex, CB: Cerebellum, HY: Hypothalamus, HP: Hippocampus, PM: Pons-Medulla, ST: Striatum. PZ 1, PZ 15, and PZ30 means treatment with *Plumbago zeylanica* for 1 day, 15 days and 30 days respectively. NQ 1, NQ 15 and NQ 30 means treatment with naphthoquinone respectively for 1 day, 15 days and 30 days.

Table 5: Effect of PZ and NQ treatment on the level of dopamine and its metabolites in brain tissue.

	DOPAMINE (ng/g of wet tissue)							
	CON	VEHICLE	PZ 1	PZ 15	PZ 30	NQ 1	NQ 15	NQ 30
CC	689 ±60	680 ±75	694 ±67	729 ±26	715 ±140	706 ±62	920 ±33 *	721 ±144
CB	1828 ±383	1969 ±522	2025 ±405	2070 ±364	2025 ±405	2053 ±508	2294 ±498	1907 ±234
HY	4293 ±607	4319±714	4408 ±557	5366 ±1021	4608 ±595	4733 ±1062	5820 ±1328	4833 ±1081
HP	1219 ±177	1374 ±330	1505 ±215	1472 ±203	1386 ±170	1714 ±425	1778 ±139*	1445 ±179
PM	676 ±75	688 ±89	674 ±79	779 ±128	675 ±78	693 ±119	935 ±328	683 ±87
ST	6370 ±1065	6318 ±832	6184 ±1031	7180 ±970	6144 ±784	6269 ±820	8205 ±568*	6286 ±782

Values are expressed as Mean ± SEM. The '*' represent statistical significance compared with control at p<0. 05. CC: Cerebral cortex, CB: Cerebellum, HY: Hypothalamus, HP: Hippocampus, PM: Pons-Medulla, ST: Striatum. PZ 1, PZ 15, and PZ30 means treatment with *Plumbago zeylanica* for 1 day, 15 days and 30 days respectively. NQ 1, NQ 15 and NQ 30 means treatment with naphthoquinone respectively for 1 day, 15 days and 30 days.

Dopamine and its metabolites

The dopamine, 3, 4 di-hydroxy phenyl acetic acid and homovanillic acid from various groups are summarized in figure 68-85 as well as in table 12, 13 and 14 with mean ± SEM. One-day treatment with PZ or NQ didn't alter the dopamine, DOPAC and HVA level in the brain. After 15 days treatment PZ did not alter the dopamine, DOPAC and HVA level in any of the regions whereas NQ treatment increased the dopamine level in cerebral cortex (F = 4. 3, df 7, 40), hippocampus (F = 2. 9,df 7,40) and striatum (F = 3. 24, df 7,40). However, the rest of the regions remain unaffected. The 30 days of PZ and NQ treatment none of the region showed variation. At this dosage, PZ even after repeated exposure did not interfere with the dopamine, 3, 4 di-hydroxy phenyl acetic acid (DOPAC) and homovanillic acid.

DISCUSSION

There are reports available to support that the components in the herbs can cross blood brain barrier to affect the central nervous system. For instance, *Ocimum sanctum* (OS) can act as an anti-stressor. Further the anti-noise stressor activity of OS has already been reported for the central cholinergic system (Sembulingam *et al.*, 2005). Kumar *et al*, (2002) reported that Indian *Hypericum perforatum* treatment (doses of 50 and 200 mg/kg) significantly decreased the levels of serotonin and its metabolite 5-hydroxy indole acetic acid and 5-HT turnover in all the brain regions (hypothalamus, hippocampus, striatum, pons-medulla and frontal cortex). Moreover, they also reported that, it significantly augmented the levels of norepinephrine and its metabolite methylhydroxy phenyl glycol (MHPG) and norepinephrine turnover in all the brain regions studied. In this study, epinephrine (15 days with NQ) as well as norepinephrine (15 days with both NQ and PZ) increased in striatum whereas the dopamine increased in cerebral cortex, hippocampus and striatum (with NQ 15 days). Noteworthy that in spite of 30 days of repeated PZ and NQ administration most of the brain region showed no variation in most of the neurotransmitters studied. This may be due to habituation (a stimulus, when repeated over and over leads to the gradually disappearing response) which is associated with the decreased release of neurotransmitter from the pre synaptic terminal because of decreased intracellular calcium by inactivating calcium channels (Ganong, 2001).

The serotonin level in rats showed alteration in cerebellum (NQ fed 15 days) and in striatum (Both PZ and NQ fed) in this study. Though the level of serotonin increased no alteration in HPA activity was observed as indicated by the corticosteroid level probably these regions may not be involved in HPA axis regulation.

In the present study, the NQ as well as PZ during repeated exposure affected specifically the neurotransmitters in striatum. The effects of a 50% ethanol extract of the root of *Plumbago zeylanica* was investigated (Bopaiah and Pradham, 2001) on central nervous system in rats and showed an enhancement of the spontaneous ambulatory activity without inducing stereotypic behavior. In these animals the neuro chemical estimations by Bopaiah and Pradham, (2001) revealed an elevated level of dopamine and homovanillic acid in striatum compared to the control rats. From these results, they concluded the extract possess the stimulatory properties and this might be mediated by dopaminergic mechanisms in the rat brain. In this study, though PZ and NQ were used, the homovanillic acid level was not altered irrespective of duration and whether PZ or NQ. The possible reason behind this was they used a very high dose of PZ (100,200 and 300mg/KG body weight) whereas the dosage used in this study was only 2mg/kg. It is essential to point out that the LD_{50} dose for PZ reported is 65mg/Kg by Premakumari *et al.*, (1977)

and 16mg/kg b. w. (LD_{50}) was reported by SivaKumar *et al.*, (2005). However, the dosage used by them are far high from LD 50 dose in the literature, as well as from the dose used in the present study and hence the results.

CONCLUSION

Administration of the ethanoloic extract of the *P. zeylanica* (and naphthoquinone) altered the neurotransmitter profile in few specific regions of Wistar rat brain and striatum was found to be affected more.

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