Research Article

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ALTERATIONS IN NEUROBEHAVIORAL AND BRAIN NEUROTRANSMITTERS BY *ALOE VERA* (L.) BURM.F AND VITAMIN E

Nuzhat Sultana*, Rahila Najam
Department of Pharmacology, Faculty of Pharmacy, University of Karachi, Karachi-75270, Pakistan

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***Corresponding author**
E-mail: nuztsultana@gmail.com
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ABSTRACT
The purpose of the study was to detect the concentrations of noradrenaline (NA), dopamine (DA), serotonin (5-HT)), and their metabolites (3, 4-hydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) in mice brain after the long-term administration of *Aloe vera* (leaf gel) and vitamin E. Control group was treated with 0.9% saline and treated groups were administered *Aloe vera* leaf gel (500 mg/70kg) and vitamin E (400 IU/70 kg) orally according to the body weight of mice for 30 days daily. After the administration of drug, all groups of animals were killed by decapitation and samples of brain were removed and analyzed after homogenization. Significant changes and alterations in brain biogenic amines can be suggested that the drugs may have potential and use for the treatment of psychotropic diseases and anxiety.
Keywords: *Aloe vera*, anxiolytics, brain biogenic amines, HPLC-EC, mice brain, vitamin E.

INTRODUCTION

Herbal drugs are the sources to treat injury and illness and a type of healer rather than use of modern pharmaceutical medicines. Naturally occurring drugs have been used for several millions of years[1]. Because herbal drugs are non-toxic and safer than pharmaceutical medicines[2].

Aloe vera (L.) Burm.f [3] family *Liliacea* has thin, clear and tasteless gel[4] that contains polysaccharides, aloesin[5], glycoprotein[6], flavonoids[7-8], amino acids[9], steroids[10], resin, saponins[2] and vitamins A , C and E[11].

Aloe vera mucilage consists of at least 20 different amino acids[10], cellulose, hemicelluloses and mannans[12], bradykinase[6], steroids sisosterol, cholesterol, lupeol and campesterol[10,13].

Acemannan act as an immune stimulant against psoriasis vulgaris[4]. *Aloe vera* helps in chronic wound healing[14]. Emodin has a strong laxative action but removed during manufacturing[15] found in adult plant of *Aloe vera*[16]. Aloin also increases the peristaltic movement by preventing the re-absorption of water produces laxative effect[17]. *Aloe vera* provides analgesic[18], anti-oxidative[1], anti-microbial[20, 16], anti-pruritic activities[21]; stimulate uterine contraction[22] and hypoglycemic effect[23].

Memory, learning, behavior, voluntary movement, mood, sleep and attention are the main functions of the dopamine. Dopamine is a neurotransmitter as well as a precursor of noradrenaline and adrenaline[24]. Noradrenaline can stimulates a sense of wellbeing and in stressful situation create a euphoric effect. Monoamine oxidase is an enzyme catalyzes the dopamine into DOPAC and 3-methoxytyramine (3-MT). These metabolites are degraded into homovanillic acid (HVA). 5HT or Serotonin is important for behavior, mood, sleep/wake cycle, movement, sexuality, and pain response and endocrine and cardiac functions.

Vitamin E acts as a natural antioxidant[25] is a group of fat-soluble vitamin consists of 8, in which α- Tocopherol a biologically active[26]. Vitamin E deficiency can cause retinopathy and erythrocyte hemolysis[27].

It responsible to stops the reactive oxygen production in biological membranes and inhibits propagation of free radical damage[28]and protect the cell membranes from oxidative damage which has neurological functions as well[29]. In addition, vitamin E is a platelets aggregation inhibitor.

MATERIALS AND METHOD

Animals

Long-term dosing of *Aloe vera* and vitamin E was carried out on albino mice of either sex weighing from 25 – 30 gm at 22 ± 1 ^{o}C with 12 hours light / dark cycle i.e. light on from 08.00 a.m to 08.00 p.m at the Department of Pharmacology, University of Karachi and had access to water and food. All animals were divided into three groups, one group served as control, while other two groups received *Aloe vera* and vitamin E. All procedures and protocols followed were in accordance with guiding principles in the care and use of animals, Helsinki declaration, 1964[30].

Dosing protocol

The daily dosing of *Aloe vera* (leaf gel) and vitamin E for the detection of concentrations of brain biogenic amines were carried out for a period of 30 days in dose of 500 mg/70 kg orally[31] and vitamin E in the dose of 400 IU/70 kg orally[32] respectively according to the body weight of animal. 0.9% saline (NaCl) was administered to control animals group by the same route as the treated groups.

Materials

Aloe vera was purchased from the market and used as a tested drug. Extraction medium selected as a homogenizing medium consisting of Perchloric acid, Sodium metabisulphite, EDTA, Cystein and Deionized water.

For the analysis by high-performance liquid chromatography (HPLC) buffer solution was required

consisted Dihydrogen phosphate, 10% Methanol, EDTA, Octyle sulphate sodium (purchased from Sigma-Aldrich Chemical Company Inc, USA), Deionized water and then filtered using vacuum filtration system with Polyethersulfone (PES) membrane - pore size 0.22µm (purchased from Techno Plastic Products (TPP), Switzerland)[33].

Method

Preparation of Brain samples for Neurotransmitters analysis

Mice control and tested groups (25 – 30 gm) were killed by decapitation and brains were immediately dissected on ice[34]. The brains were immediately taken and frozen at −76°C. Place the brains in tared vials for weighing. Samples were homogenized at room temperature, using extraction medium according to the weight of brains and centrifuged at 1000 rpm for 5 min three times. Supernatant was filtered. The filtrate was stored at -76 °C for analysis.

HPLC-EC assay

For the detection of concentrations of noradrenaline (NA), dopamine (DA), dioxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA) and 5-hydroxytryptamine (5-HT) using high performance liquid chromatography with Electrochemical Detection (HPLC–EC) technique were used after administration of *Aloe vera*, vitamin E and control groups. In chromatographic system mobile phase carries liquid through immobile, stationary phase. Sample components become separated by these mobilities differences from each other through the column, a narrow tube packed with stationary phase.

Statistics

All results were expressed as average value ± standard deviation (St.Dev). The significance of difference between averages was determined and data obtained from present study was analyzed. P-value < 0.01 was considered significant and P-value < 0.001 was considered highly significant, following the one way ANOVA[35-36].

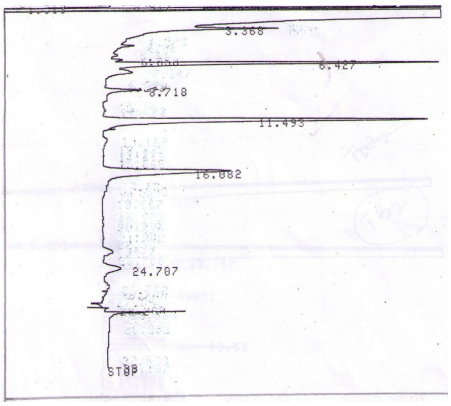

Figure 1: HPLC-EC Chromatogram Traces showing different brain Biogenic amines in control group

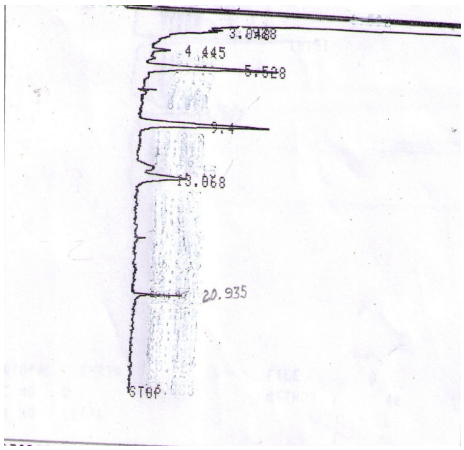

Figure 2: HPLC-EC Chromatogram Traces showing different brain Biogenic amines in *Aloe vera* group

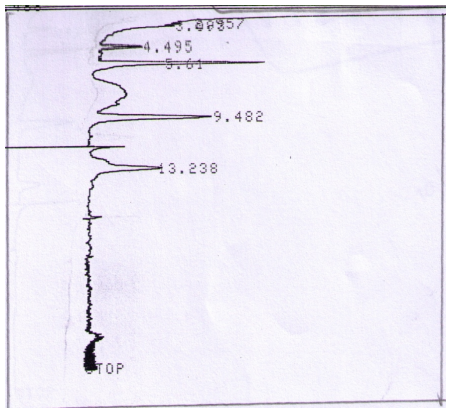

Figure 3: HPLC-EC Chromatogram Traces showing different brain Biogenic amines in Vitamin E group

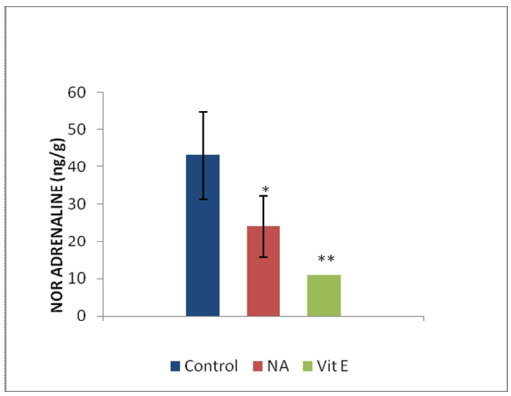

Figure 4: Effect of *Aloe vera* on Noradrenaline in mice brain n = 10, Average value ± St .Dev, *p < 0.01 as compared to control group, **p < 0.001 as compared to control group, Significant difference by Newman keuls test

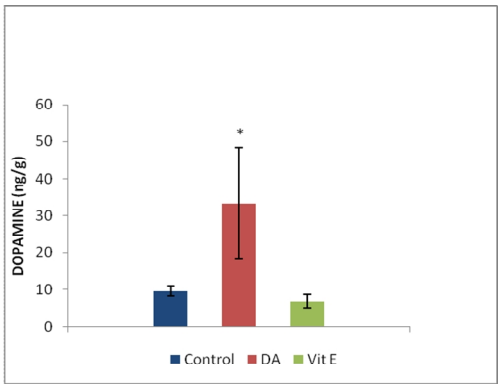

Figure 5: Effect of *Aloe vera* on Dopamine in mice brain
n = 10, Average value ± St .Dev, *p < 0.01 as compared to control group, **p < 0.001 as compared to control group, Significant difference by Newman keuls test

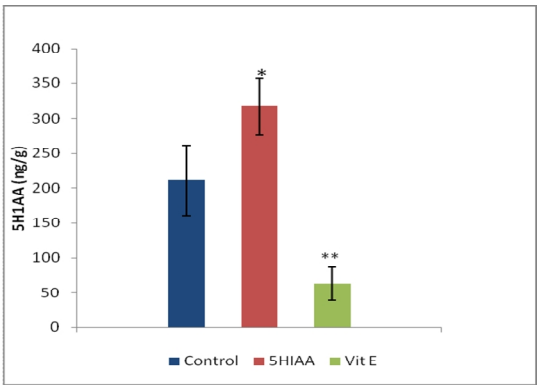

Figure 7: Effect of *Aloe vera* on 5H1AA in mice brain
n = 10, Average value ± St .Dev, *p < 0.01 as compared to control group, **p < 0.001 as compared to control group, Significant difference by Newman keuls test

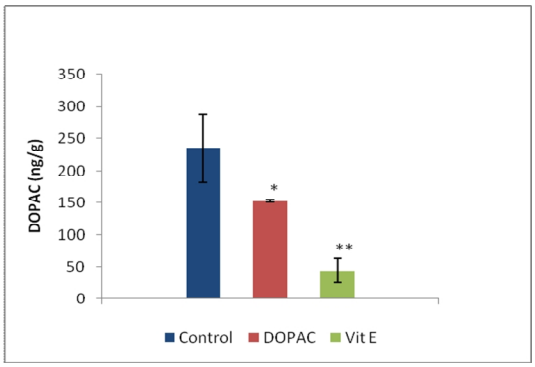

Figure 6: Effect of *Aloe vera* on DOPAC in mice brain
n = 10, Average value ± St .Dev, *p < 0.01 as compared to control group, **p < 0.001 as compared to control group, Significant difference by Newman keuls test

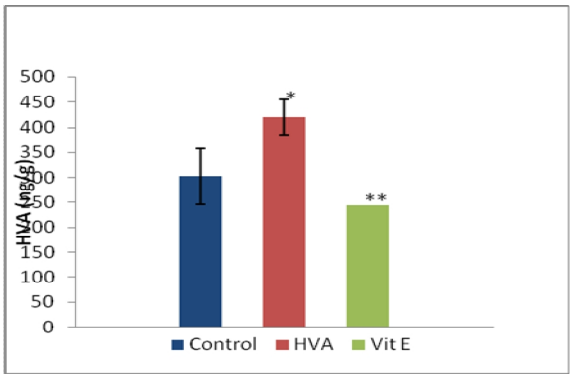

Figure 8: Effect of *Aloe vera* on HVA in mice brain
n = 10, Average value ± St .Dev, *p < 0.01 as compared to control group, **p < 0.001 as compared to control group, Significant difference by Newman keuls test

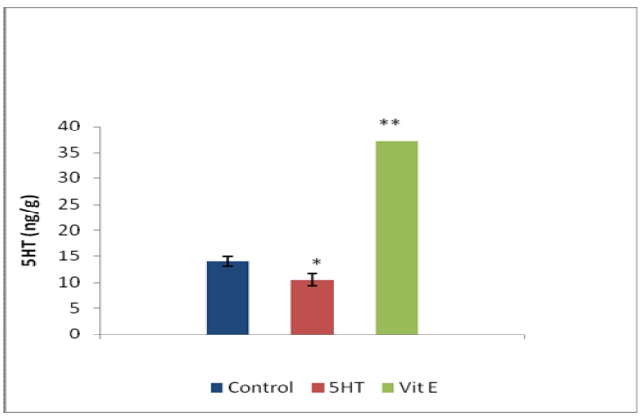

Figure 9: Effect of *Aloe vera* on 5HT in mice brain
n = 10, Average value ± St .Dev, *p < 0.01 as compared to control group, **p < 0.001 as compared to control group, Significant difference by Newman keuls test

RESULTS

Neurotransmitters and their metabolites concentrations level were detected by HPLC-EC (high performance liquid chromatography with Electrochemical Detection).

The data showed major significant differences (Newman; 1939, Keuls; 1952) of concentrations of neurotransmitters and their metabolites after long – term administration of Aloe *vera* and vitamin E.

Figures 1, 2, 3, 4, 5, 6, 7, 8 and 9 showed the results of treated (*Aloe vera* and vitamin E) and control groups on the concentration of NA, DA, DOPAC, 5HIAA, HVA and 5HT after long – term dosing. The One-way ANOVA revealed *Aloe vera* and vitamin E effects on concentrations of Noradrenaline (NA), Dopamine (DA), 3,4-Dihydroxyphenylacetic acid (DOPAC), 5-Hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA) and 5-hydroxytryptamine (5HT) in the whole brain of mice and chromatogram traces.

Effect on Noradrenaline

Figure 4, Post-hoc analysis by Newman – Keuls test showed significant decrease in Noradrenaline, i.e. 24.30 ± 8.25 (ng/g) after long – term administration of *Aloe vera* and was compared with control and vitamin E animal groups, i.e. 43.92±11.6 and 10.79±0.008 (ng/g) respectively by One-way ANOVA.

Post-hoc analysis by Newman – Keuls test showed highly significant decrease in Noradrenaline, i.e. 10.79±0.008 (ng/g) after long – term administration of vitamin E and compared with control and *Aloe vera* animal groups, i.e. 43.92 ± 11.6 and 24.30 ± 8.25 (ng/g) respectively by One-way ANOVA.

Figure 4 animals after long – term dosing of *Aloe vera* showed significant decrease in Noradrenaline in comparison to control and vitamin E animals groups in the whole brain.

Effect on Dopamine

Figure 5, Post-hoc analysis by Newman – Keuls test showed significant increase in DA, i.e. 33.34 ± 15.05 (ng/g) after long – term dosing of *Aloe vera* and compared with control and vitamin E animal groups, i.e. 9.72 ± 1.33 and 6.94±1.83 (ng/g) respectively by One-way ANOVA.

Post-hoc analysis by Newman – Keuls test showed non-significant decrease in DA, i.e. 6.94±1.83 (ng/g) after long – term dosing of vitamin E and compared with control and *Aloe vera* animal groups, i.e. 9.72 ± 1.33 and 33.34 ± 15.05 (ng/g) respectively by One-way ANOVA.

Figure 5 animals after long – term dosing of *Aloe vera* showed significant increase in dopamine in comparison to control and vitamin E animals groups in the whole brain, and vitamin E showed decrease in levels of dopamine.

Effect on DOPAC

Figure 6, Post-hoc analysis by Newman – Keuls test showed significant decrease in DOPAC, i.e. 153 ± 2.0 (ng/g) after long – term dosing of *Aloe vera* and compared with control and vitamin E animals group, i.e. 235 ± 52.38 and 44.4±19.0 (ng/g) respectively by One-way ANOVA.

Post-hoc analysis by Newman – Keuls test showed highly significant decrease in DOPAC, i.e. 44.4±19.0 (ng/g) after long – term dosing of vitamin E and compared with control and *Aloe vera* animals group, i.e. 235 ± 52.38 and 153 ± 2.0 (ng/g) respectively by One-way ANOVA.

Figure 6 animals after long – term dosing of *Aloe vera* showed significant decrease in DOPAC in comparison to control and vitamin E animals groups in the whole brain.

Effect on 5-HIAA

Figure 7, Post-hoc analysis by Newman – Keuls test showed significant increase in 5-HIAA, i.e. 316.60 ± 39.9 (ng/g) after long – term dosing of *Aloe vera* and compared with control and vitamin E animals groups, i.e. 211.40 ± 50.35 and 62.8±23.7 (ng/g) respectively by One-way ANOVA.

Post-hoc analysis by Newman – Keuls test showed highly significant decrease in 5-HIAA, i.e. 62.8±23.7 (ng/g) after long – term dosing of vitamin E and compared with control and *Aloe vera* animals groups , i.e. 211.40 ± 50.35 and 316.60 ± 39.9 (ng/g) respectively by One-way ANOVA

Figure 7 animals after long – term dosing of *Aloe vera* showed significant decrease in 5-HIAA in comparison to control and vitamin E animals groups in the whole brain.

Effects on HVA

Figure 8 Post-hoc analysis by Newman – Keuls test showed significant increase in HVA, i.e. 419.30 ± 34.87 (ng/g) after long – term dosing of *Aloe vera* and compared with control and vitamin E animals groups, i.e. 302.02 ± 56.15 and 242.72±0.008 (ng/g) respectively by One-way ANOVA.

Post-hoc analysis by Newman – Keuls test showed highly significant decrease in HVA, i.e. 242.72±0.008 (ng/g) after long – term dosing of vitamin E and compared with control and *Aloe vera* animals groups, i.e. 302.02 ± 56.15 and 419.30 ± 34.87 (ng/g) respectively by One-way ANOVA.

Figure 8, Post-hoc analysis by Newman – Keuls test showed that animals after long – term dosing of *Aloe vera* show significant decrease in HVA in comparison to control and vitamin E animals groups in the whole brain.

Effects on 5HT

Figure 9, Post-hoc analysis by Newman – Keuls test showed significant decrease in 5HT, i.e. 10.44 ± 1.16 (ng/g) after long – term dosing of *Aloe vera* and compared with control and vitamin E animals groups, i.e. 13.97 ± 0.88 and 37.11±0.008 (ng/g) respectively by One-way ANOVA.

Post-hoc analysis by Newman – Keuls test showed highly significant increase in 5HT, i.e. 37.11±0.008 (ng/g) after long – term dosing of vitamin E and compared with control and *Aloe vera* animals groups, i.e. 13.97 ± 0.88 and 10.44 ± 1.16 (ng/g) respectively by One-way ANOVA.

Figure 9 animals after long – term dosing of *Aloe vera* showed significant decrease in 5HT in comparison to control and vitamin E animals groups in the whole brain.

DISCUSSION

All medicines have adverse and toxic effects even newly designed drugs also possess side effects as well as they are expensive. Herbal medicines are more effective, potent, and inexpensive and possess lesser side effects[37].

Aloe vera is widely recognized effective herbal medicine used for its anti-inflammatory, anti-pruritic, analgesic, antioxidant, antiseptic and antibacterial effects. It can stimulate skin growth and repair; inhibit viral replication and helps in digestion. Its antioxidative property is due to inhibition of peroxidation and has a high free radical scavenging activity.

In this study results indicate that concentration of Noradrenaline (NA) was slightly decreased in certain brain circuits but the level of HVA was increased, indicating that probably the metabolism of NA is increased. NA is related to depression, so can also play a role in depression.

Aloesin a constituent of *Aloe vera* can inhibit the DOPA oxidase and tyrosine hydroxlase[38]. Tyrosine hydroxlase enzyme is responsible for the conversion of tyrosine into L – DOPA, Dopamine and then noradrenaline. According to the results low level of NA could be due to the *Aloe vera*-Aloesin, which blocks the biosynthesis of NA by the inhibition of Tyrosine hydroxlase.

Dopamine is secreted in several areas of the brain, the substantia nigra and the ventral tegmental area[24]. In schizophrenia, excessive amount of DA is secreted by the substantia nigra. Low level of dopamine has been associated with painful symptoms in Parkinson's disease and dose-dependent increase in the concentration of dopamine (DA) is observed after the administration of analgesic drugs[39]. *Aloe vera* has an analgesic activity so increase in level of DA is contributing to analgesic effect and is consistent with our findings[40].

Long – term administration of *Aloe vera* showed a significant increase in the DA level. It is concluded that prolonged administration of *Aloe vera* can increase the striatal level of DA. Dopamine plays an important role in cardiovascular disease and can be administered in patients with cardiac failure but in lower doses[41] and it can also increase the cardiac output to improve failing heart functions.

Effects observed that the *Aloe vera* might inhibit the monoamine reuptake, by the binding to the dopamine (DA) transporters and to regulate the dopamine efflux in mice brain regions. It is concluded that *Aloe vera* acts like monoamine oxidase inhibitors (MAOIs) by preventing the activity of monoamine oxidase, thus inhibiting the breakdown of monoamine neurotransmitters. After the analysis of neurotransmitters, changes occur in the concentrations of DA, dihydroxyphenylacetic acid (DOPAC), hydroxyindolacetic acid (5-HIAA), homovanillic acid (HVA), 5-hydroxyindolacetic acid (5-HIAA) and 5HT in the striatal after the long – term administration of *Aloe vera.*

In Parkinson disease, the dopaminergic neurons are destroyed or damaged, the level of dopamine drop than normal in the substantia nigra. In present study dopamine increases hence it could be beneficial in this disease as the results of *Aloe vera* shows slightly increase the level of dopamine and slightly decrease in the level of DOPAC and HVA indicating the slow metabolism of dopamine. This use of *Aloe vera* could be further investigated.

Serotonin (5HT) plays an important role in mood regulation, memory, muscle contraction and feelings of well-being and synthesized in serotonergic neurons in the CNS [42]. Result of present study indicate low level of serotonin (5HT) because 5HT is metabolized into 5HIAA and it is supported by our findings that the level of 5HIAA was also increased indicating the increased metabolism of 5HT.

Prostanoids precursor arachidonic acid is present in the extract of *Aloe vera* [43] and by the arachidonic acid pathway, dopamine and 5HT receptors are activated. In another study some neurological problems such as Bipolar disorder and Alzheimer disease are associated with the disturbance of arachidonic acid metabolism[44]. In current study dopamine is slightly increased and 5HT is slightly decreased indicating that the arachidonic acid pathway activates the dopamine and 5HT receptors but decreased level of metabolites DOPAC and HVA, also shows the slow metabolism of dopamine.

Acemannan derivative of mannan found in *Aloe vera* [45] reduces the symptoms of some neurological diseases such as anxiety and severe depression. Increase level of dopamine is one of the causes of schizophrenia [46]. Few antipsychotic drugs that block the dopamine receptor 47 are useful in the schizophrenia[48]. Antipsychotic drugs both typical and atypical, reduces the locomotor activity in animals and human being [49].

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