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# Neurotherapeutic Comparison of Aripiprazole and Ethanolic Extract of Fragaria Ananassa on Cerebrum and Amygdala of Methamphetamine Intoxicated Male Wistar Rats

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Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

## Abstract

The obvious need for other effective therapeutic medication for methamphetamine induced cerebral and amygdala toxicity have warranted this reseach. *Fragaria ananassa,* extracted ethanolically. current study looked at the neurotherapeutic comparison of the ethanolic extract of *Fragaria ananassa* on cerebrum and amygdale of methamphetamine intoxicated wistar rats. The rats were used in 8 groups. Oxidative stress markers were analysed, neurobehavioural tests were carried out, histological examination was done. SPSS version 20.0 was used to analyze the data, with a 0.05 considered significant. Group A was the control group and B received 100mg/kg of meth. Group C received received 200mg/kg of ethanolic extracts of strawberry. Group D, E, F 100mg/kg of meth and 100mg/kg of ethanolic extract of strawberry and finally 100mg/kg of meth a d trested with 200mg/kg of ethanolic extract of strawberry a d 10mg/kg of aripiprazole respectively. Correlation of the initial weight and the final weight shows an obvious increase in weight of the rats especially the control group (A) and the F, G group. The histoarchitecture showed marked degeration of neuronal cells in group B which received methamphetamine alone but knew further improvement in groups that were subsequently treated with the extract. The study further demonstrates that oxidative stress (SOD, MDA, CAT) were not significantly altered also as long as the ethanolic extracts of strawberry were administered alongside the ingested methampohetamine in line with other hypotheses.

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**Keywords:** Methamphetamine, Cerebrum, Amygdala, Wistar Rats.

## Introduction

Currently, we are in the midst of an overdose crisis in the Africa and Nigeria to be precise, Drug use is on rampage. Cocaine, heroine and methamphetamine to mention just a few.

The next generation is in huge trouble as over 41 million young people are plagued in deep meth addiction. and of course this tragic trajectory goes far beyond an opioid epidemic but also from desire of other albeit higher sources of euphoric substances. A viable solution to this deterioratipn needs to be found fast, hence the need for this research.

Several researches has been put in place to discover the effect of methamphetamine on several brain structures but much work has not been done regarding it's effect on the cerebrum and Amygdala proper.

There is a need to find alternative therapeutic help to loss of cerebral function caused by continous use of methamphetamine and so comparison will be done between a known neurotherapeutic drug (Apiriprazole) to ascertain if the ethanolic extract from *fragaria Ananassa* can serve as remedy for degeneration in both cerebrum and Amygdala function in male wistar rats. Hence, the need for this study.

Methamphetamine also known as ice or crystal meth — is a highly addictive psychostimulant drug similar to amphetamine. It has powerful euphoric effects similar to those of cocaine. But, its use can also be life-threatening. (Yu et al., 2015)

Methamphetamine increases the level of naturally occurring dopamine and nor-epinephrine in the brain. The effect lasts longer than those of cocaine, and it is cheaper and easy to make with commonly available ingredients. Street names for this drug include chalk, crank, ice, crystal meth, and speed.

According to the National Institute on Drug Abuse (NIDA), around 2.6 million people aged 12 years and older used methamphetamine in the United States in 2019. NIDA also estimated that 1.5 million Strawberry (*Fragaria ananassa Fragani)* is a reddish fruit. The garden strawberry (or simply strawberry; Fragaria × ananassa) is a widely grown hybrid species of the genus Fragaria (Manganaris et al., 2014) collectively known as the strawberries, which are cultivated worldwide for their fruit. The strawberry (*Fragaria × ananassa* Duch.) possesses a remarkable nutritional composition in terms of micronutrients, such as minerals, vitamin C, and folates, and non-nutrient elements, such as phenolic compounds, that are essential for human health. Although strawberry phenolics are known mainly for their anti-inflammatory and antioxidant actions, recent studies have demonstrated that their biological activities also spread to other pathways involved in cellular metabolism and cellular survival. (Marc et al., 2019)

Despite the wealth of research focused on various aspects of strawberry, particularly its leaves and roots, there exists a notable gap in literature concerning its fruits. Nevertheless, within certain locations, strawberry fruits and extracts finds utility in addressing infections and inflammations caused by opportunistic pathogens (Marc et al., 2019). This study endeavors to explore the neurotherapeutic comparison of Aripiprazole and ethanolic extracts of Fragaria Ananassa on Cerebrum and Amygdala of methamphetamine induced male wistar rats, thereby presenting a novel contribution to scientific inquiry.

## Materials And Method

### Procurement Of Experimental Animals

A total of Thirty-three (33) male wistar rats weighing between 130-160g obtained from the Animal House of the College of Health Sciences and Technology, would be used for this study.

They were acclimatized for 2 weeks before the commencement of study commenced,.

#### Procurement and identification of plant material

Strawberry fruits was procured from Shoprite mall in Enugu state, and were identified in the Botany department of Nnamdi Azikiwe University.

#### Housing of Experimental Animals

They were housed in well-aerated laboratory cages., under room temperature and 12hr light and 12hr dark cycle in the animal house of the Department of Anatomy Nnamdi Azikiwe University. They were fed with standard rat feed and distilled water. All experimental procedures complied with the commendations provided in the Guide for the care and use of laboratory Animals prepared by The National Academy of Sciences and published by the National Institute of Health (1985).

#### How the strawberry fruit extract is prepared

- Enough Fresh strawberry fruit will be purchased from a mall at Awka, Anambra state.
- The fruit is sliced in halves and scattered in a tray to dry. It's taken into the oven to dry it to it's very dry. This is done on high temperature. It will be checked at intervals to prevent ot from burning.
- When dry enough, we'd bring it out to cool before taking to the dry mill to grind the dry strawberry to fine powder.

Now, it will be really for use by diluting with appropriate amount of distilled water.

#### Determination of Lethal Dose (Acute Toxicity Study)

The median lethal dose (LD 50) of methamphetamine was carried out in the Department of Human Physiology Laboratory, Faculty of Basic Medical Science, Nnamdi Azikiwe University, Nnewi Campus. This would be determined using the method of Lorke (1983). In this study, a total of 12 rats would be used and would receive graded doses of the extract via oral route.

#### Induction with methamphetamine

The animals was induced methamphetamine intra peritoneally according to Farshid et Al., 2015. This procedure was

carried out in the morning preferably.

The solution was injected into the peritoneal cavity of rats using a 26-gauge needle and a 1 mL syringe. The injection is given to avoid any injury to the organs. The animals will then be monitored for any adverse reactions such as breathing difficulties, bleeding or swelling at the injection site, slowlyor changes in behavior. After injection, the animals wll be provided with food and water ad libitum. Blood glucose levels will be measured after 24 hours, and animals with blood glucose levels greater than 250 mg/dL will be considered.

## Experimental Design

After acclimatization, the animals were grouped into eight groups (1, 2, 3, 4, 5, 6, 7 and 8) of between four to ix rats in a group.

- Group A: Control. was fed distilled water and feed only
- Group B: was administered 100mg/kg of methamphetamine
- Group C: was administered 200mg/kg of ethanolic extracts of strawberry.
- Group D: was administered 100mg/kg Apiriprazole (a standard drug) only
- Group E: was administered 100mg/kg of methamphetamine and tested with Apiriprazole (a standard drug) only
- Group F: was administered 100mg/kg of methamphetamine and treated immediately with 50mg/kg of ethanolic extract of strawberry.
- Group G: was administered 100mg/kg of methamphetamine and treated immediately with 100mg/kg of ethanolic extract of strawberry.
- Group H: Will be administered 100mg/kg of methamphetamine and treated immediately with 200mg/kg of ethanolic extract of strawberry and 10mg/kg of Apiriprazole.

### Histological study

Tissues (cerebrum and Amygdala) were fixed in 10% formol saline and were dehydrated in four (4) concentrations of Isopropyl alcohol, i.e. 70%, 80%, 90%, 100% for 1hour each and then cleared in xylene before embedding in molten paraffin wax to remove the isopropyl alcohol. Micro sections of 5micrometer using Leica RM 212 Rt. Rotary Microtome, tissues was stained using Haematoxylin and Eosin (H&E) to demonstrate general tissue structure. Tissues sectioned will be examined and interpreted using Leica DM 750 binocular microscope with photomicrographic facilities and then photomicrographed by a histopathologist (Ahmed, 2016)

### Statistical analysis

The experimental result were expressed as the mean± SD. SPSS version 23 was used. The data was evaluated using student t-test with one way analysis of variance (ANOVA), p-value of $<0.05$ was considered as statistically significant.

# Results

## Morphological Finding

**Table 1.** Result of weight change

| GROUP | INITIAL WEIGHT (Mean ± SD) | FINAL WEIGHT (Mean ± SD) | P-Value |
|---|---|---|---|
| **A** | 105.0 ± 15.06 | 217.50 ± 14.85 | 0.009 |
| **B** | 151.50 ± 16.26 | 202. 50 ± 31.82 | 0.09 |
| **C** | 112.50 ± 3.62 | 175.00 ± 29.70 | 0.05 |
| **D** | 115.50 ± 0.71 | 202.50 ± 4.95 | 0 |
| **E** | 132.50 ± 0.71 | 174. 00 ± 7.07 | 0.01 |
| **F** | 109.00 ± 1.41 | 185.0 ± 1.41 | 0 |
| **G** | 132.00 ± 2.83 | 193.50 ± 2.12 | 0 |
| **H** | 143.50 ± 0.71 | 154.00 ± 9.89 | 0.14 |

The result of the body weight showed that rats in te control group A had significant weight gain at the final stage of the research compared to the initial stage. All the rats in the experimental group B to H also experienced some increase in weight at final stage. But not all are statistically significant. Group C, D, E, F, and G that received 200mg/kg of ethanolic extracts from strawberry, administered with 100mg/kgof aripiprazole only, administered with 100mg/ of methamphetamine plus standard drug, F administered 100mg of meth and treated with 50mg/kg of ethanolic extract of strawberry, 100mg/kg of strawberry and H administered with 100mg/kg of meth treated with 200mg/kg of ethanolic extract of strawberry plus 10mg/kg of aripiprazole respectively was a statistically significant increase in the body weight.

## Oxidative Stress Result

Table 2 shows the mean and standard deviation of the oxidative stress parameters

**Table 2.** Oxidative Stress Findings

| PARAMETER | GROUP | MEAN | P-Value |
|---|---|---|---|
| **MDA** | A | 5.88 ± 0.62 | |
| | B | 5.44 ± 0.32 | 0.43 |
| | C | 5.49 ± 0.45 | 0.55 |
| | D | 5.28 ± 0.27 | 0.34 |
| | E | 5.35 ± 0.21 | 0.04 |
| | F | 4.36 ± 0.23 | 0.08 |
| | G | 3.96 ± 0.50 | 0.08 |
| | H | 3.30 ± 0.32 | 0.03 |
| **SOD** | A | 17.19 ± 2.06 | |
| | B | 15.78 ± 1.22 | 0.41 |
| | C | 17.76 ± 6.32 | 0.91 |
| | D | 19.18 ± 0.38 | 0.31 |
| | E | 15.32 ± 1.73 | 0.43 |
| | F | 24.16 ± 3.77 | 0.16 |
| | G | 18.54 ± 8.87 | 0.85 |
| | H | 24.49 ± 1.73 | 0.06 |
| **CAT** | A | 23.32 ± 1.25 | |
| | B | 19.51 ± 1.37 | 0.1 |
| | C | 20.28 ± 5.43 | 0.52 |
| | D | 15.67 ± 1.06 | 0.02 |
| | E | 18.77 ± 0.78 | 0.05 |
| | F | | 0.79 |
| | G | | 0.56 |
| | H | | 0.53 |

## Oxidative Stress

Results were presented as mean ± SD of rats in each group. The results shows that the rats in the experimental group B, C, D, E, F, G H were not under oxidative stress when compared to rats in the control group A. There were little significant differences in the oxidative stress parameters analysed. For Maloaldehyde (MDA), in group E & H showed significant difference from the control. Tere were no differences in the Superoxide dismutase (SOD) and in the catalayse (CAT), group D & E, there were significant differences from the control. Oxidative stress is generally defined as the deterioration of the balance between oxidant and antioxidant mechanism. Oxidative stress products damage many biological molecules including proteins, nucleic acids and lipids. (Biren et al 2012)

This correlates with a study by (Buxton et al.,2008) a study investigating young mice found that there was a decrease in motor activity, nervous system activity, and increased behavioural pattern.

**Table 3.** Morris Water Maze (MWM) Test Findings

| GROUP | INITIAL VALUE (s) | FINAL VALUE (s) | P-VALUE |
|---|---|---|---|
| A | 35.71 ± 7.00 | 15.50 ±12.02 | 0.09 |
| B | 34.00 ± 4.24 | 77.82 ±35.11 | 0.111 |
| C | 21.00 ± 5.66 | 15.31 ±3.73 | 0.18 |
| D | 22.00 ±12..73 | 24.28 ± 24.02 | 0.46 |
| E | 24.50 ± 12.02 | 26.68 ± 16.40 | 0.45 |
| F | 10.50 ± 3.53 | 33.42 ± 25.80 | 0.17 |
| G | 54.00 ± 1.41 | 11.83 ± 4.48 | 0.41 |
| H | 15.50 ± 0.71 | 8.30 ± 0.276 | 0.34 |

Results are presented in Mean ± SD. The results of Morris water maze test (MWM) test shows that rats in the control group spent lesser time to locate to escape stage during the final test compared to the initial test although the difference was not statistically significant.

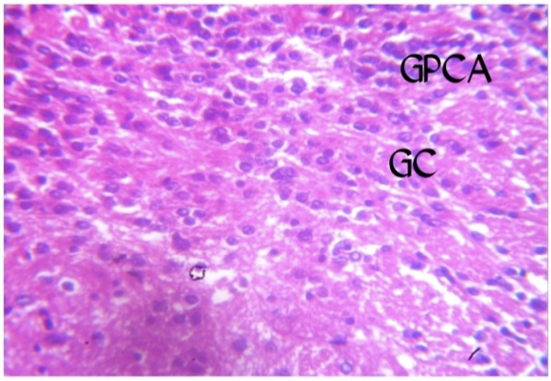
A distinctive factor in In this procedure is, the animal cannot know where the platform is hidden in trial 1 of each day. However, once it finds the platform, it can generally encode this new location in one trial. This is shown by the animal finding the platform much faster on trial 2 and subsequent trials (Steele et al., 1999)

In my research, the same was seen in rats in groups C, G and H that received 200mg/kg of ethanolic extracts of strawberry, 100mg/kg of meth treated with 100mg/kg of extract and 100mg/kg of meth treated with 200mg/kg of extract and 10mg/kg of aripiprazole respectively.

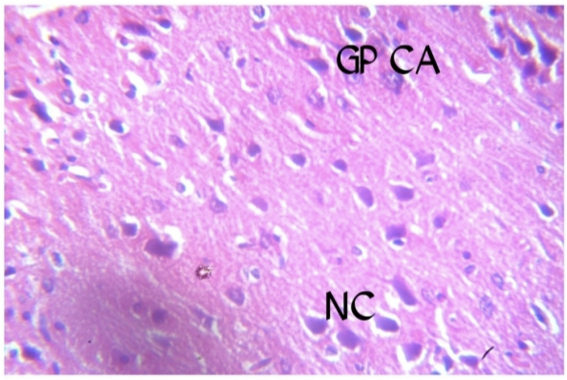
Actually, that of G and H were statistically significant. However, no significant difference was observed in values from rats in group B, D, E and F which received 100mg/kh of meth only, D which received 100mg/kg of Aripiprazole (our standard drug) recorded no significant difference, E which received 100mg/kg of methamphetamine and tested with aripiprazole,

was also not significantly different as the standard drug doused the effect of the methamphetamine effects. F which received 100mg/kg of meth tested with 200mg/kg of ethanolic extract of strawberry and 10mg/kg of aripiprazole respectively was not badly affected too.

## Histological Findings

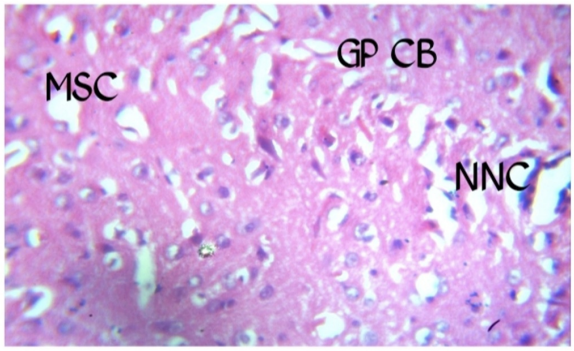



Photomicrograph of group CA section of amydala (x100 X400/(H/E) shows numerous aggregate of active granular cells (GC) and other neuronal cell that are normal .

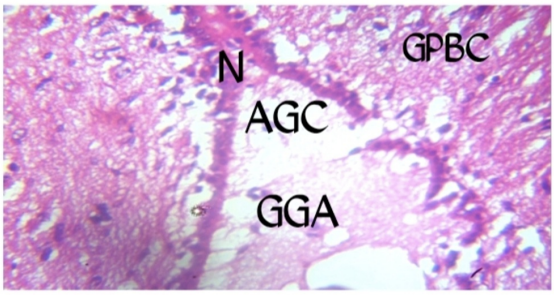



Photomicrograph of group CA section of cerebral cortex (x400)(H/E) shows cerebral cortex with active normal neuronal cells(NC)

**Plate 1.** Photomicrograph of A (control section) of cerebral cortex and Amygdala

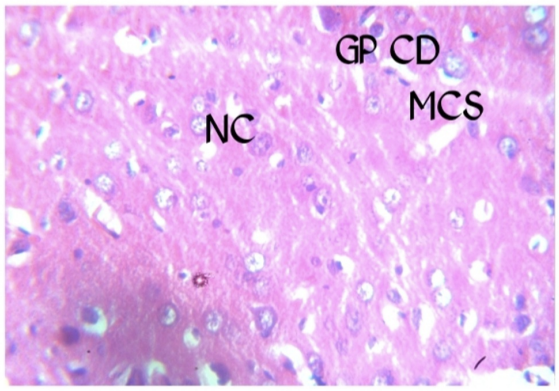



Photomicrograph of group section of cerebral cortex induced with metamphetanine only (x400)(H/E) shows severe degeneration with severe micro cystic space (MS) and necrotic neuronal cells (NNC)

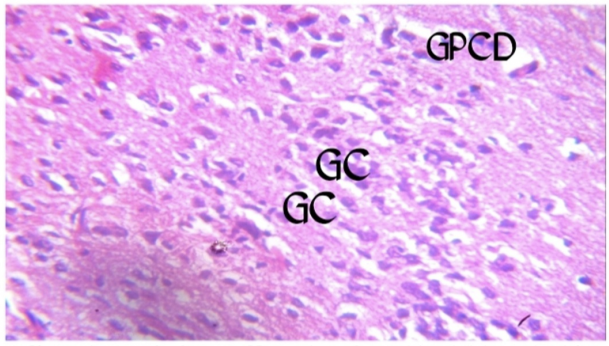



Photomicrograph of group CB section of amydela inused with metamphetanine only (x100 X400/(H/E) shows severe degeneration with severe necrotic (N) and attrophy of granular cell (AGC) and severe ground glass apperance (GGA)

**Plate 2.** Photomicrograph of Group B section of cerebral cortex and Amygdala was administered 100mg/kg of methamphetamine

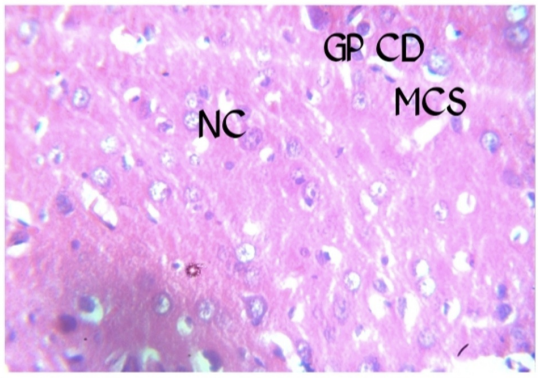



Photomicrograph of group CD section of cerebral cortex administered with atorvasation (x400)(H/E) shows cerebral cortex with active normal neuronal cells(NC)

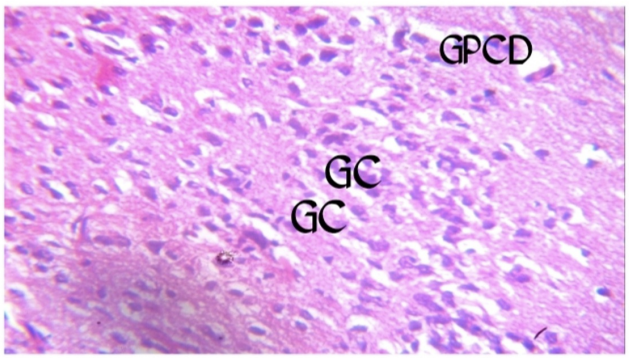



Photomicrograph of group CD section of amydala administered with attrovasation x100 X400/(H/E) shows moderate aggregate of active granular cells (GC) that are well outlined

**Plate 3.** Photomicrograph of group C administered 200mg/kg of ethanolic extracts of strawberry.

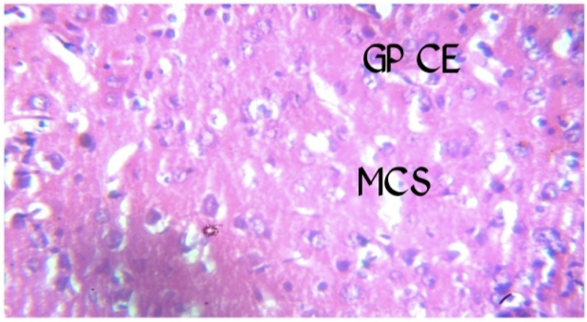



Photomicrograph of group CD section of cerebral cortex administered with atorvasation (x400)(H/E) shows cerebral cortex with active normal neuronal cells(NC)

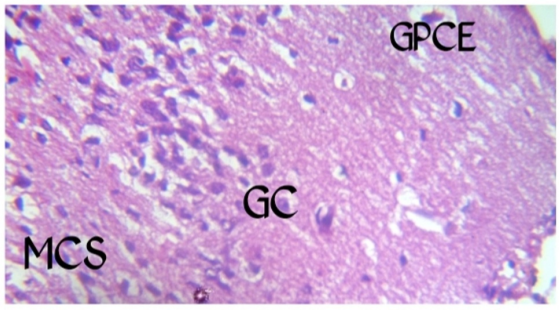



Photomicrograph of group CD section of amydala administered with attrovasation x100 X400/(H/E) shows moderate aggregate of active granular cells (GC) that are well outlined

**Plate 4.** Photomicrograph of Group D and was administered 100mg/kg Apiriprazole (a standard drug) only

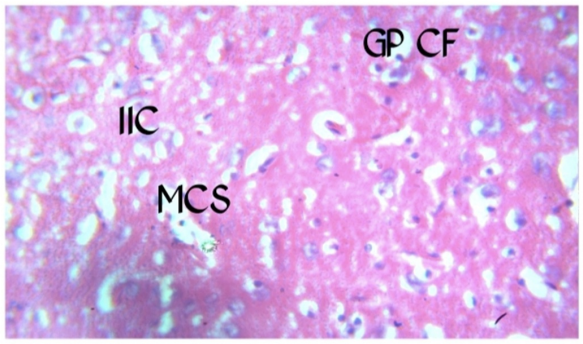



Photomicrograph of group CE section of cerebral cortex indused with metamphetanine and attrovasation (x400)(H/E) shows moderate regeneration with mild micro cystic spaces otherwise normal withn active normal neuronal cells(NC)

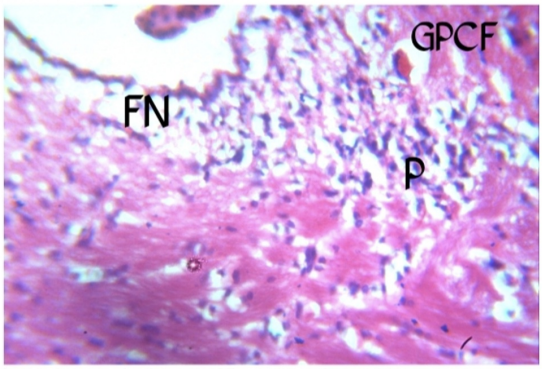



Photomicrograph of group CE section of amydala indused with metamphetanine and atorvasation x100 X400/(H/E) shows mild pyknotic granular cells (GC) with mild micro cytstic spaces (MCS)

**Plate 5.** Photomicrograph of E was administered 100mg/kg of methamphetamine and tested with Apiriprazole (a standard drug) only

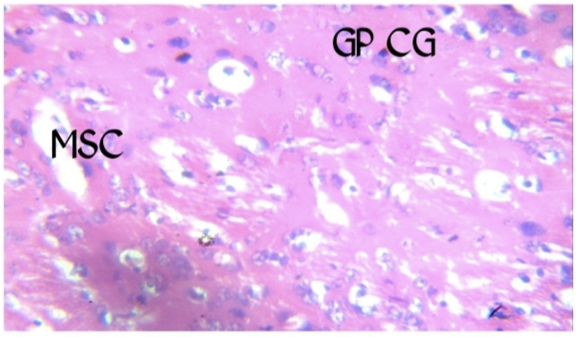



Photomicrograph of group CF section of cerebral cortex induced with metamphetanine and low dose extract (x400)(H/E) shows mild regeneration with moderate micro cystic space (MS) and moderate infilteration of inflammatory cell (IIC)

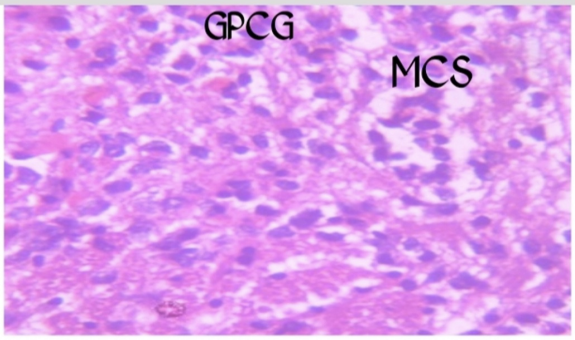



Photomicrograph of group CF section of amydala indused with metamphetanine and low dose extract x100 X400/(H/E) shows mild regeneration with moderate pyknotic (P) granular cells (GC) with moderate fatty necrosis (FC)

**Plate 6.** Photomicrograph of group F was administered 100mg/kg of methamphetamine and treated immediately with 50mg/kg of ethanolic extract of strawberry.

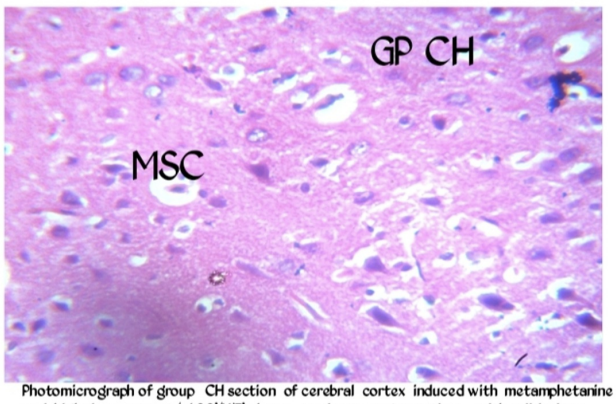



Photomicrograph of group CG section of cerebral cortex induced with metamphetanine and medium dose extract (x400)(H/E) shows moderate regeneration with mild micro cystic space (MS)

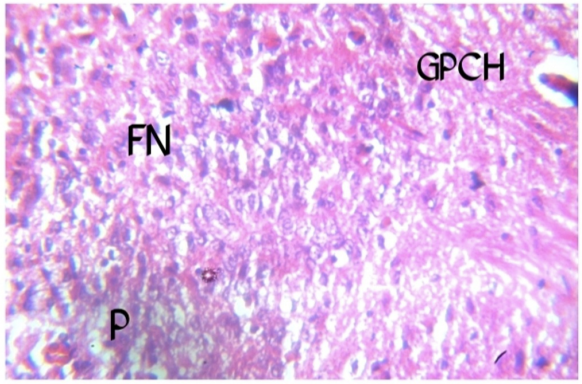



Photomicrograph of group CG section of amydala indused with metamphetanine and medium dose extract x100 X400/(H/E) shows moderate regeneration with mild micro cystic spaces (MCS)

**Plate 7.** Photomicrograph of group G was administered 100mg/kg of methamphetamine and treated immediately with 100mg/kg of ethanolic extract of strawberry.




Photomicrograph of group CH section of cerebral cortex induced with metamphetanine and high dose extract (x400)(H/E) shows moderate regeneration with mild micro cystic space (MS)




Photomicrograph of group CH section of amydala indused with metamphetanine and high dose extract x100 X400/(H/E) shows moderate regeneration with mild fatty necrosis (FN) and pyknotic (P) granular cells in some areas

**Plate 8.** Photomicrograph of group H Will be administered 100mg/kg of methamphetamine and treated immediately with 200mg/kg of ethanolic extract of strawberry and 10mg/kg of Apiriprazole.

## Conclusion

The findings of this study shows that the extract at the test dose have ameliorative, and neurotherapeutic effects on cerebrum and amygdala of methamphetamine intoxicated male wistar rats. (Giamperi *et al.,* 2012) had said that strawberries contain phytochemicals with potent antioxidant and anti inflammatory properties, such as anthocyanins, caffeic acid, ellagic acid and flavonoids including tannins, catechins, quertin, kaempferol, and gallic acid derivatives. They also contain vitamin C and e carotenoids. It has been demonstrated that dietary supplementation wit the antioxidant curcumin reduces oxidative stress (Martinez-Morua et al., 2012) and reduces brain damage by increasing levels of the brain-derived neurotropic factor in obese mice.

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