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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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Abstract

The obvious need for other effective therapeutic medications for methamphetamine-induced cerebral and amygdala toxicity has warranted this research. *Fragaria ananassa,* extracted ethanolically. The current study looked at the neurotherapeutic effects of the ethanolic extract of *Fragaria ananassa* on the cerebrum and amygdala of methamphetamine-intoxicated Wistar rats. The rats were divided into 8 groups. Oxidative stress markers were analysed, neurobehavioural tests were carried out, and histological examination was done. SPSS version 20.0 was used to analyze the data, with a significance level of 0.05 considered significant. Group A was the control group, and B received 100mg/kg of meth. Group C received 200mg/kg of the ethanolic extract of strawberry. Groups D, E, and F received 100mg/kg of meth and 100mg/kg of the ethanolic extract of strawberry, and, finally, 100mg/kg of meth was treated with 200mg/kg of the ethanolic extract of strawberry and 10mg/kg of aripiprazole, respectively. The correlation between the initial weight and the final weight showed an obvious increase in the weight of the rats, especially in the control group (A) and the F and G groups. The histoarchitecture showed marked degeneration 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 markers (SOD, MDA, CAT) were not significantly altered as long as the ethanolic extracts of strawberry were administered alongside the ingested methamphetamine, in line with other hypotheses.

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1. Introduction

Methamphetamine (contracted from N-methylamphetamine) is a potent central nervous system (CNS) stimulant that is mainly used as a recreational drug and less commonly as a second-line treatment for attention deficit hyperactivity disorder and obesity. ([1]) Methamphetamine was discovered in 1893 and exists as two enantiomers: levomethamphetamine. ([note 2])

Methamphetamine is known to possess a high addiction liability (i.e., a high likelihood that long-term or high-dose use will lead to compulsive drug use) and high dependence liability (i.e., a high likelihood that withdrawal symptoms will occur when methamphetamine use ceases). Withdrawal of methamphetamine after heavy use may lead to post-acute withdrawal syndrome, which can persist for months beyond the typical withdrawal period. Methamphetamine is neurotoxic to human midbrain dopaminergic neurons and, to a lesser extent, serotonergic neurons at high doses. ([1])([3]).

Aripiprazole, sold under the brand names Abilify and Aristada, is an atypical antipsychotic. ([4]) It is primarily used in the treatment of schizophrenia, obsessive compulsive disorder (OCD), and bipolar disorder; other uses include as an add-on treatment in major depressive disorder, tic disorders, and irritability associated with autism. Aripiprazole is taken by mouth or via injection into a muscle. A Cochrane review found low-quality evidence of effectiveness in treating schizophrenia. ([5])

Aripiprazole was approved for medical use in the United States in 2002. It is available as a generic medication. In 2020, it was the 89th most commonly prescribed medication in the United States, with more than 8 million prescriptions. It is on the World Health Organization's List of Essential Medicines. (World Health Organization, 2023).

Aripiprazole is primarily used for the treatment of schizophrenia or bipolar disorder.

It is used as maintenance therapy; it is useful for the prevention of manic episodes but is not useful for bipolar depression. ([6]).

Thus, it is often used in combination with an additional mood stabilizer; however, co-administration with a mood stabilizer increases the risk of extrapyramidal side effects. ([6])

Strawberry (or simply strawberry; *Fragaria ananassa*) ([7]) is a widely grown hybrid species of the genus Fragaria, collectively known as the strawberries, which are cultivated worldwide for their fruit. The fruit is widely appreciated for its characteristic aroma, bright red color, juicy texture, and sweetness. It is consumed in large quantities, either fresh or in such prepared foods as jam, juice, pies, ice cream, milkshakes, and chocolates. Artificial strawberry flavorings and aromas are also widely used in products such as candy, soap, lip gloss, perfume, and many others.

In addition to being consumed fresh, strawberries can be frozen or made into jam or preserves, as well as dried and used in prepared foods, such as cereal bars. Strawberries and strawberry flavorings are a popular addition to dairy products, such as strawberry milk, strawberry ice cream, strawberry milkshakes/smoothies, and strawberry yogurts. ([7])

Cerebrum, the largest and uppermost portion of the brain, consists of the cerebral hemispheres and accounts for two-thirds of the total weight of the brain. One hemisphere, usually the left, is functionally dominant, controlling language and

speech. The other hemisphere interprets visual and spatial information.

A thick band of white matter that connects the two hemispheres, called the corpus callosum, allows the integration of sensory input and functional responses from both sides of the body.

Amygdala is a small, almond-shaped structure inside your brain. When it comes to your survival, your amygdala and limbic system are extremely important. These are parts of your brain that automatically detect danger. They also play a role in behavior, emotional control, and learning. ([8])

Going by all these, the essential properties discovered from *Fragaria ananassa* ethanolic extract need to be evaluated to compare its neurotherapeutic effects as compared to Aripiprazole.

2. Materials and Method

The study was carried out in the laboratory unit of the Department of Anatomy, Nnamdi Azikiwe University, Nnewi, Anambra State, Southeastern Nigeria. Ethical approval was obtained from the committee of the faculty. All chemicals and materials used were obtained for the study. *Fragaria ananassa* was bought in a generous quantity from a mall at Awka and was washed, dried, ground, and extracted.

Experimental animals and design

After acclimatization, the animals were grouped into eight groups (1, 2, 3, 4, 5, 6, 7, and 8), with four to six rats in each 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 of Aripiprazole (a standard drug) only. Group E: was administered 100mg/kg of methamphetamine and tested with Aripiprazole (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 Aripiprazole.

Neurobehavioural tests were carried out on the animals (hanging wire test, Morris water test, and open field test) and were analysed accordingly.

All administrations were made orally with syringes and cannula. The rats were sacrificed after a month of administration. Following the sacrifice, blood samples of each rat were collected and biochemical analyses were run; oxidative stress parameters were evaluated.

Statistical analysis

Statistical analysis was done using SPSS software version 23. Analysis of variance (ANOVA) and student's t-test were used in comparison of means of biochemical parameters, with $p<0.05$ considered to be statistically significant.

3. Results and Discussion

(Table 1) shows the distribution of the mean weight of the rats in the various groups before and after the administration of methamphetamine, and *Fragaria ananassa* is shown in (Table 1). During acclimatization, the rats in the groups showed healthy features and normal cognitive neurobehavioural characteristics. Following administration, the results of the body weight showed that rats in the 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 groups B to H also experienced some increase in weight at the final stage.

Table 1. Distribution of the mean weight of the rats in the various groups before and after the administration of the test substance

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

But not all are statistically significant. Groups C, D, E, F, and G that received 200mg/kg of ethanolic extracts from strawberry, administered with 100mg/kg of aripiprazole only, administered with 100mg/kg of methamphetamine plus standard drug, F administered 100mg of meth and treated with 50mg/kg of ethanolic extract of strawberry, and H administered 100mg/kg of meth treated with 200mg/kg of ethanolic extract of strawberry plus 10mg/kg of aripiprazole, respectively, showed a statistically significant increase in body weight.

Table 2. Distribution by mean levels of oxidative stress parameters of various groups, B, C, D compåred to normal group A

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	

Results were presented as mean ± SD of rats in each group. The results show that the rats in the experimental groups B, C, D, E, F, G, H were not under oxidative stress when compared to rats in the control group A. This is because there were no significant differences in the oxidative stress parameters analysed, Malondialdehyde (MDA), Superoxide dismutase (SOD), and catalase (CAT). Oxidative stress is generally defined as the deterioration of the balance between oxidant and antioxidant mechanisms. Oxidative stress products damage many biological molecules, including proteins, nucleic acids,

and lipids.

Table 3. Mean distribution for the Morris water maze test before and after the administration of the test substance.

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
H	15.50 ± 0.71	8.30 ± 0.276	0

Morris described the basic procedures in 1984 (ref.[1]). Results are presented in mean ± SD. The results of the Morris water maze (MWM) test show that rats in the control group spent less time to locate the escape stage during the final test compared to the initial test, although the difference was not statistically significant.

A distinctive factor in this procedure is that 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.

4. Conclusion

With proper administration of *Fragaria ananassa,* one can significantly restore the cerebral and amygdala effects caused by methamphetamine intoxication.

By increasing the level of knowledge about the effects of these hard drugs, their preventions, and therapeutic steps, affected individuals can be helped in preventing more severe stages of this form of brain damage. ([2]) 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, quercetin, kaempferol, and gallic acid derivatives. They also contain vitamin C and e carotenoids.

Limitation

The study has been undertaken in Wistar rats, and the findings may not be totally representative of what could occur in human subjects.

A clinical trial on the neurotherapeutic role of ethanolic extracts of *Fragaria ananasa* employing laid-down processes, procedures, and ethical requirements is recommended.

Statements and Declarations

Financial support and contribution

None

Compliance with ethical standards

The authors declare that there is no conflict of interest.

Notes and References

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[2] Enantiomers are molecules that are mirror images of one another; they are structurally identical, but of the opposite orientation. Levomethamphetamine and dextromethamphetamine are also known as L-methamphetamine, (R)-methamphetamine, or levomethamphetamine (International Nonproprietary Name (INN) and D-methamphetamine, (S)-methamphetamine, or methamphetamine (INN), respectively.

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