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Antidepressant Effect of Methanol Fruit Extract of *Capsicum annuum* in Mice

Esther Badugu Patrick[1*], Danjuma Mallam[1] and Seth Hassan Albarka[1]

[1]Department of Pharmacology and Toxicology, Kaduna State University, Kaduna State, Nigeria.

Authors' contributions

This work was carried out in collaboration between all authors. Author EBP designed the study, wrote the protocol, conducted the experiment and checked the data collected, assisted in statistical analysis and prepared the manuscript initially. Author DM collected the data and reviews, made statistical analysis of the data and author SHA conducted the experiment, collected the data and reviews. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To determine the antidepressant potential of methanol fruit extract of *Capsicum annuum* in Mice.
Methodology: Force Swim Test (FST), Tail Suspension Test (TST) and Open Field Test (OFT) were used. Immobility time in both FST and TST was determined by randomly dividing 30 mice into five (5) groups of six (6) mice each. Group 1 received saline, Group 2, Imipramine (15 mg/kg), Group 3, 4, and five were treated with 500 mg/kg, 1000 mg/kg, and 2000 mg/kg of methanol extract of fruits of *Capsicum annuum* respectively. In the OFT, 25 mice were divided into five(5) groups of five (5) mice each; Group 1 received normal saline, group 2, Diazepam (0.5 mg/kg), group 3,4 and 5 were treated with 500 mg/kg, 1000 mg/kg and 2000 mg/kg of methanol fruit extract of *C. annuum respectively.*
Results: Imipramine, and the doses of the methanol fruit extract significantly reduced the immobility time when compared with a normal saline group ($p \leq 0.05$) in the mice FST and TST. The effect of

**Corresponding author: E-mail: patrickebadugu75@yahoo.com;*

the extract was dose-dependent; 2000 mg/kg produced the highest reduction. In the Open field test (OFT), the number of square crossing showed no significant difference between Diazepam (0.5 mg/kg) and all the doses of the extract administered. This implied that the extract did not act as a stimulant.

Conclusion: The decrease behavioural despair in this study suggests that *Capsicum annuum* may be a promising candidate for the management of depression. The antidepressant like activity may be attributed to the presence of anti-inflammatory and antioxidant flavonoids and triterpene in the plants given the role of inflammation and oxidative stress in depression. Further work will be carried out to validate this result.

Keywords: Depression; antidepressants; Capsicum annuum; antidepressant screening model.

1. INTRODUCTION

Depression is a disorder that affects a patient's ability to work and function in society; it leads to increase morbidity and consequently increased use of health resources. Other than its chronic nature, symptoms associated with this mental disorder are often recurring and life-threatening. Depression ranks among the most prevalent mental diseases worldwide [1] with a prevalence of 4.7% worldwide [2]. According to the estimations of the World Health Organization, depression will be the second leading cause of disability in 2020 [3]. Depression is also the major cause of morbidity worldwide. Depressive patients have a 2-4 fold increased the risk of developing cardiovascular diseases, and 10-15% of individuals with major depression commit suicide [4]. It also leads to serious social and educational impairments and is associated with an increased rate of smoking, substance abuse and obesity [5].

Several drugs have been developed to treat depression.Unfortunately these drugs have some draw backs; they work in few people, response rates within 6 to 8 weeks are around 70% while remission rates are sometimes considerable lower and they still have too many side effect (tiredness, restlessness, sexual dysfunction, weight gain and some cases aggressiveness) [6], they have modest efficacy, it takes too long before it works [7], meaning there is need for newer agents. There are various sources of new lead compounds for depression among which are medicinal plants [8]. One of such plant that may be useful is *Capsicum* annuum.

The present study was undertaken to screen the antidepressant effect of methanol extract of *Capsicum annuum* in mice due to the urgent need for better agents to treat this disorder. *Capsicum annuum* has a high concentration of vitamin C [9]. Vitamin C is a cofactor that aids in the synthesis of neurotransmitters; Norepinephrine and Serotonin [10]. The plant contains Vitamin E and glutathione [9,11] both of these have an antioxidant effect and also have free radicals scavenging effect.

Capsicum annuum fruit extract, therefore, may be beneficial for patients with depression due to the low level of Norepinephrine and Serotonin and the role of free radicals in depression. Although there is no folkloric claim on the use of *Capsicum annuum* for depression, the information above regarding the role of vitamin C in the synthesis of neurotransmitters and the fact that it contains a significant concentration of other anti-oxidants. *Capsicum annuum* is, therefore, a promising prospect for the treatment of depression.

2. MATERIALS AND METHODS

2.1 Collection and Identification of Plant Materials

The fresh *Capsicum annuum* fruit was obtained from Central Market Kaduna, Kaduna State, Nigeria in November 2017. It was authenticated by Mallam U.S. Gallah, a taxonomist in the Department of Biological Sciences, Kaduna State University, Kaduna. A voucher specimen number of 9918 was assigned.

2.2 Preparation of Extract

The fresh fruit was washed with water and air-dried under shade for seven days. It was size-reduced mechanically using a clean ceramic pestle and mortar to obtain the 150 g powder. One hundred and fifty grams (150 g) of the powdered fruit was extracted by cool maceration in 400ml of methanol for 48 hours after which, it was filtered via suction using a Buckner funnel. The extract was concentrated in a Rotary evaporator at a temperature of 40^{o}C and 0.08

Mpa pressure for 2 hours. The concentrated extract was finally dried in an oven for 14 days at 40ºC and was kept at 4ºC in a refrigerator in an amber airtight container until needed for use. The percentage yield of the extract was calculated to be 39.6% w/w.

2.3 Animals Used

Swiss Albino Mice of either sex weighing 18-25 g were obtained from the Animal House of the Department of Pharmacology and Toxicology, Kaduna State University. The animals were maintained under standard environmental condition of humidity, temperature, and 12 hours light/dark cycle, with access to standard diet and water *ad libitum*. The animals were acclimatized for two weeks before the commencement of the study. A standard protocol was drawn up by current guidelines for the care for laboratory animals and ethical guidelines for investigations of experiments in conscious animals.

2.4 Acute Toxicity Studies (LD_{50})

The Oral and intraperitoneal median lethal dose (LD_{50}) was carried out using Lorke's method [12] using mice. The method consists of two phases. In the first phase, nine (9) mice were divided into three groups of three mice each. The oral median lethal dose (LD_{50}) was determined by administration of *Capsicum annuum* extract at doses of 10 mg/kg, 100 mg/kg, and 1000 mg/kg orally and observed for signs of toxicity and death within 24 hours. In the second phase, three mice were treated with three doses of 1600 mg/kg, 2900 mg/kg and 5000 mg/kg of extract orally respectively.

The same procedure was used to determine the intraperitoneal (ip) median lethal dose (LD_{50}) by administering the extracts intraperitoneally (ip). The LD_{50} was determined by calculating the geometric mean of the lowest dose that caused death and the highest dose for which the animals survive.

2.5 Animal Models of Depression

2.5.1 Forced Swim Test (FST)

The force swim test (FST) was performed using standard procedure [13]. Thirty (30) mice were randomly allocated into five (5) groups of six (6) mice each. Group 1 was treated with normal saline and served as a negative control, Group 2 were treated with Imipramine (15 mg/kg) and served as positive control. Group 3, 4, and five were treated with 500 mg/kg, 1000 mg/kg and 2000 mg/kg of methanol extract of *Capsicum annuum* respectively. All administrations were carried out intraperitoneally before the test.

Force swim test was conducted by placing Mice individually in a plastic cylindrical tank (46 cm tall × 20 cm in diameter) filled with tap water (25 ± 1ºC) to a depth of 20 cm. Thirty (30) minutes post-treatment Mice were placed in the plastic tank and observed for 6 minutes. During this period, the immobility time of the animals was recorded within the last 4 minutes. Mice were considered immobile when they remained floating without struggling and making only slight movements necessary to maintain the head above the water. Fresh water was used for each mouse and mice were dried at the end of each test period.

2.5.2 Tail Suspension Test (TST)

The Tail Suspension Test (TST) was performed according to reported procedure [14]. Thirty (30) mice were randomly allocated into five (5) groups of six (6) mice each; Group 1 was treated with normal saline and served as negative control, Group 2 were treated with Imipramine (15 mg/kg) and served as positive control.G roup 3, 4, and 5 were treated with 500 mg/kg, 1000 mg/kg and 2000 mg/kg of methanol extract of *Capsicum annuum* respectively. All administrations were carried out intraperitoneally before the test.

Thirty (30) minutes post-treatment in all groups; mice were individually suspended vertically at about 15 cm on a tail suspension test apparatus with an adhesive tape place 1cm away from the tip of the tail. Immobility period was recorded within 6 minutes of the test period. Mice were considered to be immobile when they did not show any movement of the body and hanged passively. Before the introduction of each mouse, the space used was cleaned with 70% ethanol to prevent behavioural changed brought about by olfactory cues.

2.5.3 Open field test

The Open Field Test (OFT) was performed using a modified version of Walsh and Cummins [15]. Twenty-five (25) mice were randomly allocated into five (5) groups of five (5) mice each; Group 1 were treated with normal saline and served as negative control, group 2 were treated with Diazepam (0.5 mg/kg), and served as positive

control, group 3,4 and 5 were treated with 500 mg/kg, 1000mg/kg and 2000 mg/kg of methanol fruit extract of *C.annuum respectively.* All administrations were carried out intraperitoneally before the test.

At about 30 minutes post-treatment in all groups, mice were individually placed in the centre square of the open field test apparatus and observed for various behaviours. The following parameters were measured; latency to leave centre square, the number of squares crossed (with all four paws), and time spent in the centre square, all these were recorded within 5 minutes testing period. At the end of each test period, the mouse is removed and the box cleaned with 70% ethanol before placing the next mouse. The same procedure was repeated until all the 25 mice were tested.

2.6 Phytochemical Screening

The methanol extract of *Capsicum annuum* was subjected to preliminary phytochemical analysis according to reported procedure [16,17].

2.6.1 Test for carbohydrates

Molisch Test

To a small portion of the extract in a test tube, few drops of Molisch reagent were added and concentrated sulphuric acid was added down the side of the test tube to form a lower layer, a reddish-coloured ring at the interphase confirmed the presence of carbohydrates.

Fehling Test

To a small portion of the extract in a test tube, 5ml of an equal mixture of Fehling solution A and B was added and boiled on a water bath, red brick precipitate indicate the presence of reducing sugar.

2.6.2 Test for glycosides

To a portion of the extract, 5ml of dilute sulphuric acid was added and boiled on a water bath for 10-15 minutes; this was then cooled and neutralized with 20% KOH. It was then divided into two portions:

To the first portion, 5 ml of a mixture of Fehling's solution A and B were added and boiled; a red brick precipitate shows the release of reducing sugar as a result of hydrolysis of Glycoside.

To the second portion, about 3 ml of Ferric chloride solution was added; a green to blue colour will be produce because of the release of phenolic aglycones.

2.6.3 Test for free anthraquinones (Bontrager's test)

To a portion of the extract in a dry test tube, 5 ml of chloroform was added and was shaken for at least 5 minutes. This was filtered and the filtrate was shaken with an equal volume of 10% ammonia solution, bright pink colour in the aqueous (upper) layer indicates the presence of free anthraquinones.

2.6.4 Test for combined anthracene derivatives (Modified Bontrager's test)

A small portion of the extract in a test tube was boiled with 5ml of 10% hydrochloric acid for 2-3min. This would hydrolyze the glycosides to yield aglycones, which are soluble in hot water. This was then filtered, and the filtrate was cooled and extracted with 5 ml of benzene. The benzene layer was pipetted and shaken gently in a test tube with half of its volume of 10% ammonium hydroxide. If the lower ammonium layer becomes rose pink to cherry red, the drug contains anthraquinones derivative (free or in the combined state).

2.6.5 Test for unsaturated steroid and triterpenes

Lieberman Buchard Test

To a portion of the extract, an equal volume of acetic acid anhydride was added and mixed gently. 1ml of concentrated sulphuric acid was added down the side of the test tube to form a lower layer. Colour changes were observed immediately and over a period of one hour. Blue to blue-green colour in the upper layer and a reddish pink or purple colour indicate the presence of triterpene.

Salkowski Test for Unsaturated Sterols

To a small portion of the extract, 2-3 drops of concentrated sulphuric acid w ere added at the side of the test tube, cherry red colour at the interphase of the extract and sulphuric acid over one hour period confirmed the presence of unsaturated sterols.

2.6.6 Test for cardiac glycosides

Keller-killini Test

A portion of the extract was discovered in 1 ml of glacial acetic acid containing traces of ferric chloride solution. This was then transferred into a dry test tube, and 1ml of concentrated sulphuric acid was added down the side of the test tube, a purple-brown ring at the interphase confirmed the presence of deoxy sugars and a pale green colour in the upper acetic acid layer confirmed the presence of cardiac glycosides.

Kedde's Test

To a portion of the extract, 1 ml of 2% solution of 3,5-Dinitrobenzoic acid in 95% alcohol was added, the solution was made alkaline with 5% sodium hydroxide, the appearance of purple-blue colour, confirmed the presence of cardenolides.

2.6.7 Test for saponin glycoside

Frothing Test

About 10 ml of distilled water was added to a portion of the extract and was shaken vigorously for 30 seconds. The tube was allowed to stand in a vertical position and was observed for 30mins. A honeycomb froth that persists for 10-15 mins indicated the presence of saponin.

2.6.8 Test for tannins

Ferric Chloride Test

To a portion of the extract, 3-5 drops of ferric chloride solution were added. A greenish-black precipitate indicates the presence of condensed tannins while hydrolysable tannins give a blue or brownish-blue precipitate.

Lead Sub-Acetate Test

To a small portion of the extract, 3-5 drops of the lead sub-acetate solution were added. A colored precipitate indicated the presence of tannins.

2.6.9 Test for flavonoids

Shinoda Test

A portion of the extract was dissolved in 1-2ml of 50% methanol in the heat Metallic magnesium chips, and few drops of concentrated hydrochloric acid were added. The appearance of red colour indicates the presence of flavonoids.

Sodium Hydroxide Test

Few drops of 10% sodium hydroxide were added to the extract; a yellow colouration indicates the presence of flavonoid.

Ferric Chloride Test

Few drops of ferric chloride solution were added to a portion of the extract; a green precipitate indicates the presence of a phenolic nucleus.

2.6.10 Test for alkaloids

Mayer's Test

To a portion of the extract, few drops of Mayer's reagent were added. A cream precipitate indicates the presence of alkaloids.

Dragendoff's Test

To a portion of the extract, few drops of Dragendoff reagent were added. A reddish brown precipitate indicates the presence of alkaloids.

Wagner's Test

Few drops of Wagner's reagent were added to a portion of the extract; whitish precipitate indicates the presence of alkaloids.

Picric Acid Test

Few drops of 1% picric acid solution w ere added to a portion of the extract in a test tube; yellow colouration indicates the presence of alkaloids.

2.7 Statistical Analysis

Data were analyzed using one-way ANOVA followed by Bonferroni post hoc test for multiple comparisons. $P \leq 0.05$ was considered statistically significant. Results were reported as a mean ± standard error of the mean.

3. RESULTS

3.1 Acute Toxicity Testing

The oral and intraperitoneal median lethal dose (LD_{50}) of methanol extract of *C. annuum* was calculated to be greater than 5000 mg/kg.

3.2 Animal Model of Depression

3.2.1 Forced Swim Test (FST)

Imipramine (15 mg/kg), the methanol fruit extract at 500 mg/kg, 1000 mg/kg and 2000 mg/kg group both significantly reduced the immobility time in Mice FST when compared with a normal saline group ($P \leq 0.05$). The effect of the extract was dose-dependent with 2000 mg/kg producing the highest reduction (immobility time for 2000 mg/kg.100 mg/kg and 500 mg/kg equal to; 33.7s, 45.5s, and 60.3s respectively). Imipramine (15 mg/kg) showed no statistically significant difference in immobility time when compared with 1000 mg/kg and 2000 mg/kg extract (*P*=.05). (Table 1).

Table 1. Effect of methanol fruit extract of *C. annuum*, normal saline and imipramine on immobility time in mice force swim test (FST)

Treatment	Immobility Time (s)
Normal Saline	96.00±14.93^{a}
Imipramine (15 mg/kg)	22.83 ±4.31^{b}
500 mg/kg extract	60.33 ±7.65^{c}
1000 mg/kg extract	45.50 ±2.54^{dbc}
2000 mg/kg extract	33.67 ±5.32^{ebc}

Data presented as mean ± SEM. The comparison was made using one way ANOVA, followed by Bonferroni post Hoc. Means tagged with different superscript letters alphabet are significant at P=.05. N=6

3.2.2 Tail suspension test

Imipramine (15 mg/kg), the methanol fruit extract at 500 mg/kg, 1000 mg/kg and 2000 mg/kg group both significantly reduced the immobility time in Mice TST when compared with a normal saline group (*P*=.05).The effect of the extract was dose dependent with 2000 mg/kg producing the highest reduction (mean immobility time for 2000 mg/kg, 100 mg/kg and 500 mg/kg equal to; 96.5s,97.5s, and 119s respectively). Imipramine (15 mg/kg) had shown no statistically significant difference in immobility time when compared with 1000 mg/kg and 2000mg/kg extract (*P*=.05). (Table 2).

Table 2. Effect of methanol fruit extract of *C. annuum*, normal saline and imipramine on immobility time in mice tail suspension test (TST)

Treatment	Immobility time (s)
Normal Saline	163.67±14.93^{a}
Imipramine (15 mg/kg)	70.66 ±7.69^{b}
500 mg/kg extract	119.00±8.41^{c}
1000 mg/kg extract	97.50 ±5.07^{dbc}
2000 mg/kg extract	96.50 ±9.66^{ebc}

Data presented as mean ± SEM. The comparison was made using one way ANOVA, followed by Bonferroni post Hoc. Means tagged with different superscript letters alphabet are significant at P=.05. N=6

3.2.3 Open field test (OFT)

The methanol extract at all doses (500 mg/kg, 1000 mg/kg and 2000 mg/kg) and Diazepam (0.5 mg/kg) both significantly reduced the latency time to leave the central square(mean latency time to leave center square equal to 1.6s,4s,2.8s and 5.6s for 500 mg/kg, 1000 mg/kg and 2000 mg/kg extract and 0.5 mg/kg Diazepam respectively) when compare compared with normal saline group (mean latency time to leave center square equal to24.8s) in Mice OFT (*P*=.05). There was statistical significant increase in the total number of square crossing in Diazepam (0.5 mg/kg) treated group and those treated with, 500 mg/kg, and 2000 mg/kg

Table 3. Effect of Methanol Fruit extract of *C. annuum*, Normal Saline and Imipramine on anxiety behaviours in Open Field Test(OFT) in Mice

Treatment	Latency to leave the central square (LCS)(s)	Time spend in central square (TSCS)(s)	Total Square crossing(TSC)
Normal Saline	24.80±3.92^{a}	0.60±0.40^{a}	93.40±3.76^{a}
0.05 mg/kg Diazepam	5.60 ±2.04^{b}	8.80±2.13^{b}	179.00±14.47^{b}
500 mg/kg extract	1.60 ±0.25^{cb}	10.00±2.17^{cb}	148.00±12.80^{cb}
1000 mg/kg extract	4.00 ±1.38^{db}	4.60±1.33^{ab}	137.40±10.27^{ab}
2000 mg/kg extract	2.80 ±1.32^{eb}	2.20±1.07^{ab}	164.20±7.32^{db}

Data presented as mean ± SEM. Comparison was made using one – way ANOVA, followed by Bonferroni post Hoc. Means tagged with different letters alphabet are significant at P=.05. N=5.Latency to leave the central square (LCS)(s) ,Time spent in central square(TSCS)(s), Total Square crossing(TSC).

of extract (mean total square crossing equals to 179,148, and 164 respectively) in mice OFT when compared with normal saline group (mean total square crossing equals 93). The time spent in the center square showed significant increase in the time spent in the center square in mice treated with Diazepam(0.5 mg/kg), 500 mg/kg, and 2000 mg/kg of extract(mean time spent in center square equals 8.8s,10s and 4.2s respectively) in mice OFT when compared with normal saline (mean time spent in center square 0.6s). The values for latency to leave centre square, the number of squares crossed and time spent in centre square in Diazepam (0.5 mg/kg) treated group were comparable to the groups treated with 500 mg/kg, and 2000 mg/kg of extract. (Table 3).

3.3 Phytochemical Screening

The preliminary phytochemical investigation of methanol fruit extract of *C. annuum* revealed the presence of carbohydrates, glycosides, flavonoids, tannins, alkaloids, steroids, triterpene, and cardiac glycosides (Table 4).

Table 4. Phytochemical screening of Methanol Fruit extract of *C. annuum*

Phytochemical constituent	Inference
Carbohydrates	+
Glycosides	+
Flavonoids	+
Tannins	+
Alkaloids	+
Steroids	+
Triterpene	+
Cardiac glycosides	+
Saponins	–
Free anthraquinones	–

+ and - represent presence and absence of phytochemical respectively

4. DISCUSSION

4.1 Acute Toxicity Testing

The oral and intraperitonial median lethal dose of the methanol extract of *C. annuum* fruits was calculated to be greater than 5000 mg/kg. This means the extract is relatively safe for use.

4.2 Antidepressant Activity

The two Rodent model of despair used (FST and TST) to asses antidepressant activity showed that, Imipramine, the methanol fruit extract at 500 mg/kg, 1000 mg/kg and 2000 mg/kg both significantly reduced the immobility time when compared with a normal saline group ($P \leq 0.05$). The effect of the extract was dose-dependent with 2000 mg/kg producing the highest reduction. This showed that the extract possessed antidepressants like effect, since in principle Immobility time is used to measure behavioural despair and hopelessness in depressed mice [13]. An increase in immobility time indicated depression whereas a decrease in immobility indicated antidepressant activity. This reflects behavioural despair similar to that seen in human when they are depressed. Imipramine (15 mg/kg) showed no statistically significant difference in immobility time when compared with 1000 mg/kg and 2000 mg/kg extract. Meaning an antidepressant effect comparable to that of imipramine could be achieved at a dose of 1000-2000 mg/kg of the *C. annuum* extract.

It is possible that the extract mechanism of action is similar to that of Imipramine (tricyclic antidepressants) or Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs).Since literature shows that Vitamin C (which is found in high amount in *C. annum*) plays a vital role in the synthesis of Norepinephrine and Serotonin [18].This implies that *C. annuum* likely increases the synaptic concentration of NE and 5-HT. Another possible mechanism of it likely antidepressant effect could be due to its antioxidant properties of the plant because literature shows that the plant is an excellent antioxidant [19].

4.3 Anxiolytic Activity

Open Field Test (OFT) was used to assess anxiety. It measures the evasion that rodents have for the open environment and their desire to explore a new environment. Some of the parameters used to measure locomotive activity, exploration and anxiety in the open field test include; the number of square crossing, the frequency of locomotion, number of centre square entry and duration of time spent in centre square [20]. A high frequency of these behaviours indicates increased locomotion and low level of anxiety [15]. Relating this to the results of OFT, it means the extract at all the doses used (500 mg/kg, 1000 mg/kg and 2000 mg/kg) possesses anxiolytic-like effect since it significantly reduced the latency to leave the central square, increases the number of square crossing and increases time spent in the central square when compared to normal saline ($P \leq$

0.05). The effect of 500 mg/kg and 2000 mg/ kg was comparable with that of Diazepam (0.5mg/kg). This result corresponds with the general principle used to ascertain anxiolytic property of a novel agent using OFT.

The results of the number of square crossing showed that there was no significant difference between Diazepam (0.5 mg/kg) and all the dose of the extract used. This implies that the extract is not acting as a stimulant and thus showing that the reduction in immobility time found in the study may not be due to stimulant effect but rather due to the antidepressant activity of the *C. annuum* extract.

5. CONCLUSION

The decrease behavioural despair in this study suggests that *Capsicum annuum* may be a promising candidate for the management of depression. The antidepressant like activity may be attributed to the presence of anti-inflammatory and antioxidant flavonoids and triterpene in the plants given the role of inflammation and oxidative stress in depression. Further work will be carried out to validate this result.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors at this moment declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. Experiments have been examined and approved by the appropriate ethics committee.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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