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Ameliorative Tendency of *Syzygium aromaticum* Ethanolic Extract on Cadmium-Induced Olfactory Toxicity in Rats: A Dose-Dependent Study

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Abstract

Background: Cadmium exposure is known to induce olfactory toxicity, leading to impaired olfactory function. *Syzygium aromaticum*, commonly known as clove, has been traditionally used for its medicinal properties, including antioxidant and anti-inflammatory effects. This study investigates the potential ameliorative effects of *S. aromaticum* extract on cadmium-induced olfactory toxicity in rats. **Methods:** Six groups of rats were used: control, *S. aromaticum* extract alone (10mg/kg), cadmium chloride alone (5mg/kg), and three groups receiving *S. aromaticum* extract (10, 15, and 20mg/kg) in combination with cadmium chloride (5mg/kg). Olfactory function was assessed using buried reward test. **Results:** The results were statistically significant at 95% confidence interval. The results showed that cadmium exposure significantly impaired olfactory function, which was dose-dependently improved by *S. aromaticum* extract administration. The highest dose of *S. aromaticu*m extract (20mg/kg) showed the most significant improvement in olfactory function. **Conclusion:** These findings suggest that *S. aromaticum* extract may be a potential therapeutic agent for mitigating cadmium-induced olfactory toxicity.

Keywords: *Syzygium Aromaticum*, Toxicity, Cadmium, Extract, Rats.

INTRODUCTION

Cadmium is a toxic heavy metal that can cause significant damage to various organs, including the olfactory system [1]. Exposure to cadmium has been shown to impair olfactory function [2], leading to reduced olfactory sensitivity and altered olfactory perception [1]. The olfactory system is particularly vulnerable to cadmium toxicity due to its direct exposure to the environment and the presence of olfactory receptors in the nasal cavity [3]. *Syzygium aromaticum*, commonly known as clove [4,5], has been traditionally used for its medicinal properties, including antioxidant, anti-inflammatory [6], and antimicrobial effects [7]. *S. aromaticum*, is a dried flower bud belonging to the *Myrtaceae* family [8] that is indigenous to the Maluku islands in Indonesia but has recently been cultivated in different parts of the world [9]. *S. aromaticum* is used in the cuisine of Asian, African, Mediterranean, and the Near and Middle East countries, lending flavor to meats (such as baked ham), curries, and marinades, as well as fruit (such as apples, pears, and rhubarb) [10]. *S. aromaticum* may be used to give aromatic and flavor qualities to hot beverages, often combined with other ingredients such as lemon and sugar [11]. They are a common element in spice blends, including pumpkin pie spice and other spices. The extract of *S. aromaticum* has been shown to possess significant antioxidant activity [12], which may help mitigate oxidative stress and inflammation associated with cadmium toxicity [13]. Current treatment for cadmium-induced olfactory toxicity are limited[2], and there is a need for effective and safe therapeutic agents to mitigate the effects of cadmium exposure on the olfactory system. This study aims to investigate the potential ameliorative effects of *S. aromaticum* extract on cadmium-induced olfactory toxicity in rats. The hypothesis is that, *S. aromaticum* extract would dose-dependently improve olfactory function in rats exposed to cadmium.

MATERIALS AND METHODS

Ethical approval

This Study was approved by the Research Ethics Committee of Madonna University Nigeria Ref: MAU/DRC/HD/E/PHY/2024/011.

Plant collection and preparation

The buds of *S. aromaticum* used for this study were obtained from Madonna University, Botanical Garden, Elele, Rivers State, Nigeria. The average temperature and humidity of the cloves was 26 ºC and 80% respectively.

Phytochemical screening

Using standard procedures by Ilochi and Chuemere, 2021 [14], the Phytochemical Screening of different bioactive constituents in *S. aromaticum* was done using Gas Chromatography Mass Spectrophotmetry (GC-MS) Total Antioxidant Capacity (TAC).

TOXICITY STUDY

Determination of lethal dose of *S. aromaticum*

Oral LD_{50} of *S. aromaticum*= mg/kg

Mg of *S. aromaticum* was dissolved in ml of water

Mg/ml of *S. aromaticum* was administered to the rats

1ml and 1.5ml were administered to the rats as low and high dose respectively

Acute oral toxicity (LD_{50}): 2650 mg/kg.

Determination of lethal dose of cadmium

LD_{50} of cadmium is in mg/Kg

1g of cadmium dissolved in ml of water,

Acute oral toxicity (LD_{50}):10mg/kg

Animal collection

Male Wistar rats (n=48) were used in this study. The rats were housed in a controlled environment with a 12-hour light-dark cycle and had access to food and water ad libitum. The animals were kept under room temperature and exposed to 12/12 hours' light and day cycles. The animals were grouped into experimental and control groups and housed in sanitized aluminium cages containing sawdust as bedding. All efforts were made to avoid coprophagy.

Study design

The rats were divided into six groups (n=8 per group):

1. Control group: received standard feed and water

2. *S. aromaticum* extract alone group: received 10mg/kg *of S. aromaticum* extract

3. Cadmium chloride alone group: received 5mg/kg of cadmium chloride

4. *S. aromaticum* extract (10mg/kg) + cadmium chloride (5mg/kg) group

5. *S. aromaticum* extract (15mg/kg) + cadmium chloride (5mg/kg) group

6. *S. aromaticum* extract (20mg/kg) + cadmium chloride (5mg/kg) group

Study duration

This study lasted for 28 days. For the purpose of this study, the day just before the onset of treatment was marked as day 0, while the last day of treatment was marked as day 28.

Extract Preparation

The *S. aromaticum* extract was prepared using a standardized method. Briefly, the dried buds of *S. aromaticum* were extracted with ethanol (100%), and the resulting extract was concentrated and lyophilized.

Cadmium Chloride Administration

Cadmium chloride was administered orally at a dose of 5mg/kg body weight; the administration was done using an orogastric tube. Also using protocols from earlier studies by Ilochi and Chuemere, 2024 [15].

Olfactory Function Assessment

Olfactory response was tested using the buried reward test. A wistar rat is placed in a buried reward chamber bedded with saw dust that measures 30.5x16x16 cm. in an 8cm thick bedding, the reward stimulus (chow pellet) was buried 7cm into the bedding such that it cannot be seen from the surface. the time taken for the animal to dig and sniff the chow pellet was recorded. The maximum time, recorded as latent period, was 10 minutes (600 seconds). This test was performed before (day 0) and after treatment (day 28) periods.

Statistical analysis

The data from this study was analyzed using IBM®-SPSS Version 21. The results were presented as Mean±Standard Error of Mean (SEM) and were statistically significant at 95% confidence interval compared to control.

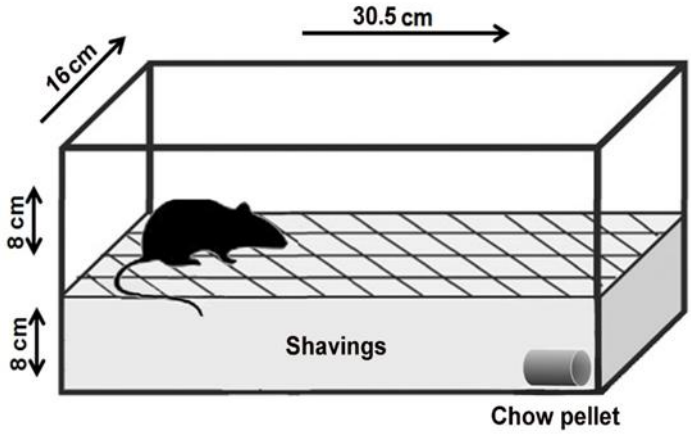

Figure 1: A buried reward chamber

RESULTS

GC-MS profiling of *S. aromaticum* extract (Table 1) revealed the presence of several bioactive compounds. The most abundant constituent was eugenol (52.53-78.67%), confirming it as the major phytochemical component. Other identified compounds included caryophyllene (3.14-37.25%), eugenyl acetate (4.05-11.77%), β-elemene (20.2%), bicyclogermacrene (13.5%), viridiflorol (11.1%), globulol (8.6%), selin-11-en-4α-ol (5.3%), humulene (4.11%), copaene (2.05%), and linoleic acid (1.2%). The presence of these compounds indicates a rich phytochemical profile with potential biological activity. GC-MS analysis of the extract showed the most abundant bioactive component is Eugenol (52.53-78.67).

The total antioxidant capacity (TAC) of *S. aromaticum* extract was evaluated using the FRAP assay (Table 2). The extract demonstrated a TAC value of 94.21 µmol Fe(II)/g, indicating strong antioxidant activity. This value was higher than that observed for vitamin C (80-90 µmol Fe(II)/g) and green tea extract (70-80 µmol Fe(II)/g), suggesting superior reducing potential.

The effects of *S. aromaticum* extract and cadmium ($CdCl_2$) on olfactory response are presented in Tables 3 and 4. Cadmium treatment alone significantly increased olfactory response from 384.20 ± 0.13 (Day 0) to

580.42 ± 0.23 (Day 28), corresponding to a 51.10% increase, indicating toxicity-induced alteration.

In contrast, co-administration of *S. aromaticum* extract mitigated cadmium-induced effects in a dose-dependent manner. The most pronounced improvement was observed in the group treated with 20 mg/kg extract + $CdCl_2$, where olfactory response decreased from 387.13 ± 0.23 (Day 0) to 180.12 ± 0.20 (Day 28), representing a -53.50% change. Lower doses (10 and 15 mg/kg) also showed protective effects, though to a lesser extent.

Overall, the findings demonstrate that *S. aromaticum* extract possesses strong antioxidant activity and exhibits significant protective effects against cadmium-induced olfactory dysfunction.

Table 1: GC-MS analysis of *S. aromaticum*

Major compounds	Presence (%)
Eugenol	52.53-78.67*
Carophyllene	3.14-37.25
Eugenyl acetate	4.05-11.77
Copaene	2.05
Humulene	4.11
Phenol, 2-methoxy-3-(2-propenyl)	64.44
β-elemene	20.2
Bicyclogermacrene	13.5
Viridiflorol	11.1
Globulol	8.6
Selin-11-en-4α-ol	5.3
Linoleic acid	1.2

Table 2: TAC of *S. aromaticum* using Ferric Reducing Ability of Plasma (FRAP) Assay

Absorbance (nm)	Trolox (Standard)	Vitamin C	Green tea extract	*S. aromaticum* extract
593	100	80-90	70-80	94.21

Table 3: Olfactory response to *S. aromaticum* and cadmium treatment

Groups	Day 0	Day 28
Control	381.40±0.12	380.21±0.01
S. aromaticum extract (10mg/kg)	386.22±0.03	210.10±0.13*
$CdCl_2$ (5mg/kg)	384.20±0.13	580.42±0.23*
S. aromaticum extract (10mg/kg) + $CdCl_2$ (5mg/kg)	381.21±0.22	372.13±0.10
S. aromaticum extract (15mg/kg) + $CdCl_2$ (5mg/kg)	381.11±0.40	240.22±0.41*
S. aromaticum extract (20mg/kg) + $CdCl_2$ (5mg/kg)	387.13±0.23	180.12±0.20*

Table 4: Percentage change in olfactory response to *S. aromaticum* and cadmium treatment

Groups	% change
Control	-0.31
S. aromaticum extract (10mg/kg)	-45.60
$CdCl_2$ (5mg/kg)	51.10
S. aromaticum extract (10mg/kg) + $CdCl_2$ (5mg/kg)	-2.40
S. aromaticum extract (15mg/kg) + $CdCl_2$ (5mg/kg)	-37.00
S. aromaticum extract (20mg/kg) + $CdCl_2$ (5mg/kg)	-53.50

From table 3 and 4, cadmium adversely affected olfactory response from 384.20±0.13 on day 0 to 580.42±0.23 on day 28 with a percentage change of 51.10, but the most significant improvement was seen in *S. aromaticum* extract (20mg/kg) + $CdCl_2$ (5mg/kg) that had an improvement in olfactory response from 387.13±0.23 on day 0 to 180.12±0.20 with a percentage change of -53.50.

DISCUSSION

Cadmium is a neurotoxic agent that has been reported to damage central and peripheral nervous system neurons [16]. The mechanism by which cadmium chloride manifests its neurotoxicity is believed to be through generation of free radicals at cellular level and subsequent peroxidation and oxidative modification of biomolecules [17]. *S. aromaticum* has been used for centuries in traditional medicine and culinary practices [18]. While its effect on various physiological systems has been studied, its impact on olfaction, or the sense of smell, is an area of growing interest [19]. The administration of *S. aromaticum* may have reversed or prevented the damaging effect of cadmium chloride on olfactory receptors, neurons or pathway [1]. The results of this study show that *S. aromaticum* extract dose-dependently improves olfactory function in rats exposed to cadmium. *S. aromaticum* contains a variety of bioactive compounds, including; Eugenol, a volatile compound responsible for the characteristic aroma and flavor of cloves; Caryophyllene, a sesquiterpene [20] with potential anti-inflammatory and antimicrobial properties; and flavonoids, a class of compounds with antioxidant and antinflammatory effects [21]. The antioxidant effect of *S. aromaticum* may be implicated in its tendency to reverse the toxicity of cadmium chloride, specifically its adverse effect on olfactory behavior. The antioxidants in *S. aromaticum,* may protect the olfactory system from damage caused by oxidative stress induced by cadmium. The highest dose of *S. aromaticum* extract (20 mg/kg) showed the most significant improvement in olfactory function. Eugenols impact on olfaction or the sense of smell has been a topic of interest. Earlier studies suggest it has a positive influence on olfaction and ability for rodents to find or trace rewarding stimuli using buried reward test. Eugenol is a volatile compound. Eugenol has been reported to have similar effect with oleic acid with respect to the sense of smell [22]. Studies on similar compounds like eugenol suggests that volatile molecules can bind to olfactory receptors, thereby influencing our sense of smell [23]. Eugenols molecular structure might allow it to interact with these receptors, although its specific effects are unclear. Eugenol has also been postulated to be useful in management of inflammation and various types of tissue trauma caused, probably, by heavy metal exposure. Its analgesic properties could indirectly affect the olfactory system by influencing neural signaling pathways [24]. However, further research is needed to understand this potential connection. The presence of other bioactive compounds in *S. aromaticum* extract may influence eugenols interaction with the olfactory system [25]. In addition, the sensitivity of individuals to any of the bioactive agents may vary, and as such, the concentration and duration of exposure may be dependent on these factors [26]. Further research should be directed towards in vivo studies to examine the effects of eugenol as well as some other bioactive agents in *S. aromaticum* on olfaction in living systems.

CONCLUSION

The study of *S. aromaticum* effect on olfaction is a complex and multifaceted topic, requiring a comprehensive approach to understand the potential interactions between this organ and the sense of smell. This study suggests that *S. aromaticum* extract may be a potential therapeutic agent for mitigating cadmium-induced olfactory toxicity. Whiule bioactive compounds in *S. aromaticum*, such as eugenol, may interact with the olfactory system, further research is necessary to fully understand the relationship between *S. aromaticum* and olfaction.

Author contributions

Ilochi Nwabunwanne Ogadinma was responsible for conceptualization of the study and writing the protocol as well as the first draft of the manuscript. Amadi Paulinus Nmereni handled the preparation of the materials, data collection and experimental analysis. Both authors provided the literature searches as well as the references and citations. Both authors read and approved the final manuscript**.**

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Conflict of interest

There is no conflict of interest.

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