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Original Article

Protective Potential of Aqueous Extract of Turmeric on the Cognitive Function of Adult Female Wistar Rats Administered with Co-Codamol

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ABSTRACT

Background and aim: Co-codamol, a widely used analgesic, has been associated with cognitive impairments. This study explored the possible neuroprotective effect of aqueous extract of turmeric against co-codamol-induced cognitive deficits in adult female Wistar rats.

Materials and methods: Twenty adult female Wistar rats were randomized into four groups (n=5 each). Groups 1 to 3received oral administration of 530mg/kg of co-codamol only, co-administration of 530mg/kg of co-codamol plus 200mg/kg of curcumin only, and 200mg/kg of curcumin only respectively for 2 weeks at a single dose of 5ml while group 4 (controls) received normal saline orally. Body weight measurements were taken and recorded, before administration and at the time of sacrifice. The rats were assessed for neurobehavioral using T-maze apparatus. The brain tissues were harvested and weighed. Data obtained were analyzed with Graph pad prism version 8.4. Results were expressed as mean ± SEM.

Results: The control group had increased body and organ weights, but there was no significant difference between the body weights of co-codamol only group and other experimental groups. Furthermore, the brain weight of rats administered with co-codamol only was significantly lower than control and other experimental groups. Neurobehavioral studies showed that the rats in the co-codamol only group had significantly longer recognition and memory times compared to control and other experimental groups ($p<0.005$).

Conclusion: These findings suggest that aqueous extract of turmeric administration could mitigate the cognitive impairment caused by co-codamol due to the changes observed in the neurobehavioral studies of the rats administered with the extract of turmeric.

Keywords:
Co-codamol; Turmeric Aqueous extract; Hippocampus

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INTRODUCTION

Drugs which are made up of a number of chemical component or compounds for therapeutic purposes may in some cases become toxic. Complications such as autoimmune phenomena and drug resistance caused by constant and indiscriminate self-medication as well as long-term use of drugs and in some cases, stopping use of drugs cause other side effects that can be more dangerous than the disease itself (Mohamed *et al.,* 2015). These reasons could be attributed to the fact that drug is a substance that brings about a change in biological function through its chemical actions (Pappano, 2009). The current prevalence of drug and substance abuse has plagued society, caused its members to lose self-consciousness and led to mental disorders, death, addiction and other hardship (Fagbe, 2019).

Co-codamol, a combination of codeine and paracetamol, is one of the most popular choices and widely prescribed for pain management (Greener *et al.,* 2018). Combining analgesics from different classes has the potential to provide adequate pain relief with reduced dose-dependent adverse events (Toms *et al.,* 2008), yet all analgesics are potentially harmful, whether because of toxicity, addiction risk or both (Raman and Fleming, 2021). Concerns have been raised over the effects of paracetamol on the cardiovascular, respiratory, renal, gastrointestinal and central nervous systems, as well as potential effects in the offspring of pregnant women ingesting paracetamol (McCrae *et* al., 2018). Codeine is available in over-the-counter combination preparations with caffeine, paracetamol or ibuprofen. However, misuse of combination products is associated with gastrointestinal hemorrhage, nephrotoxicity,

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hypocalcemia and acute hemorrhagic necrotizing pancreatitis (Barreto *et al.,* 2011; NG *et al.,* 2011).

Turmeric (*Curcuma longa*) is a widely used spice that has various biological effects, and hot aqueous extracts of turmeric exhibit potent antioxidant activity and anti-inflammatory activity (Uchio *et al.,* 2017).

Researchers are constantly exploring curcumin's potential in preventing or mitigating neurotoxicity induced by pharmaceutical agents (Rastogi *et al.,* 2014; Wang *et al.,* 2017).

The exposure of rodents to paracetamol has been reported reduce their cognitive abilities (Blecharz-Klin *et al.,* 2018; Philippot *et al.,* 2020). Same as the exposure to codeine (Achukwu *et al.,* 2019).

Furthermore, protective function of the curcumin against behavior deficits in brain injury (Wu *et al.,* 2014), 3-nitropropionic acid and lead induced neurotoxicity (Dairam *et al.,* 2007; Kumar *et al.,* 2007), have been reported. However, there is lack of study on the effect of curcumin on the rats against co-codamol-induced neurotoxicity.

Therefore, this study aimed at investigating the effect of Co-codamol on the cognitive function of adult female Wistar rats. Additionally, it explores the impact of Co-codamol and Curcumin administration on organ weight and seeks to determine whether Curcumin can mitigate the adverse effects of Co-codamol on the hippocampal regions of the brain.

MATERIALS AND METHODS

Experimental Animals, Design and Ethical Approval

A total of twenty adult female Wistar rats was obtained from the colony established at Central Animal House of the Faculty of Basic Medical Science, University of Ibadan, Ibadan, Oyo State and housed in Lead City University, Ibadan, faculty of Basic Medical and Health Sciences Central Animal House. They were randomized into four groups (n=5 each). All procedures on animal handling were conformed to the acceptable guidelines on the ethical use of animals in research and approval for the study was obtained from the Department of Human Anatomy, Lead City University, Ibadan Animal Care and Use Research Ethics Committee (LCU-REC/ANA/002/24).

The rats in groups 1 to 3 received oral administration of 530 mg/kg body weight of co-codamol only, co-administration of 530 mg/kg body weight of co-codamol plus 200mg/kg body weight of curcumin, and 200mg/kg weight of curcumin only respectively for 2 weeks via oral gavage at a single dose of 5ml while the rats in group 4 (controls) received normal saline orally. The 530mg/kg body weight of co-codamol includes 500mg/kg body weight of paracetamol (Aboshama *et al.,* 2024) and 30mg/kg body weight of codeine (Erichsen *et al.,* 2005)

Throughout the study, the rats were allowed free access to water, and solid pellet feed *ad libitum*.

Body weight measurements were taken and recorded, before administration and at the time of sacrifice.

Co-codamol

The 30/500mg of co-codamol tablets manufactured by Bristol laboratories limited, were dissolved in normal saline, and administered over the duration of experiment.

Turmeric extract Preparation

Dehydrated Curcuma longa was obtained from Agege Market, Lagos, Nigeria. The plants were then pulverized using an industrial mill, after careful inspection of the plants to ensure good quality. The turmeric powder was then dissolved in aqueous water at and boiled for 60 minutes after which the solution was then strained using a mesh strainer, to grossly remove sedimentation. This was repeated again using a filter paper, to ensure effective filtration and placed inside an oven for 1 day at 45ºc. Finally, the obtained filtrate was then stored at 4 ºc to increase shelf life and prevent degradation; (Etemadi *et al.,* 2021) and 200mg/kg was given to each rat in the co-codamol plus curcumin only and curcumin only groups.

Neuro-behavioral Test

To assess the cognitive function of the animals, a neuro-behavioral test using the T-maze was conducted post-administration, where each of the rats was placed at the base end of the maze, and an object (food) was placed at the end of one arm of the maze. The test involved observing the time taken for the movement of the rat from the base of the maze to the intersection, and their movement to either arm of the maze in recognition of the object placed in the maze, which depicts the first trial. After this, the rat was removed, and then placed back after a while; this was done to observe the time taken for the rat to navigate to where the object was previously placed, therefore allowing evaluation of their spatial learning and memory which depicts the second trial, both of which are manifestations of the hippocampus. A stopwatch timer and a camera were used to record the time taken for the rat to complete each trial (d'Isa *et al.,* 2021).

Animal Sacrifice and sample collection

At the end of the experiment, animals in the control and experimental groups were sacrificed via cervical dislocation, then the brains (cerebrum) were harvested with blunt forceps, rinsed with normal saline and weighed using a sensitive weighing scale to obtain the absolute brain Weight. The obtained values were then used to calculate the relative brain weight using the formula;

$$\frac{\text{Brain weight}}{\text{Final Body Weight}} \times 100\%$$

Data Analysis

Data obtained from organ and body weight measurements and behavioral tests in each group were analyzed using Graph pad prism version 8.4.3.686 for Windows Software (San Diego, CA,

USA). Sample means ± standard errors of means (SEM) were obtained and compared among groups using the analysis of variance (ANOVA) A probability value < 0.05 was considered to be statistically significant and results were presented in form of histograms.

RESULTS

In this study, the effect of co-administration of co-codamol and curcumin on the brain of the adult male Wistar rats was assessed by analyzing their body and organs weights (Table 1 and Figure 1). From the table, there was no significant difference between the initial body weights of the animals in control group and other groups, however, the final body weights and the weight change of animals in control group is significantly higher than other groups while there was no significant difference between the final body weights of animals in co-codamol only group, and other experimental groups, there was significant difference between the weight change of animals in co-codamol only group, and other experimental groups ($p<0.05$)

The relative brain weight of the animals in control group is significantly higher than the relative brain weight of only the rats in co-codamol only group (*****). Furthermore, the relative brain weight of the animals in co-codamol only group was significantly higher than the relative brain weight of the rats in other experimental groups **(#)** ($p<0.05$) (Figure 1).

The mean recognition time across the control and experimental groups as derived from the T-maze test is shown in Figure 2. The rats in control group had significantly shorter recognition times compared to co-codamol only, and co-codamol + curcumin groups (*****). However, the co-codamol only had significantly longer recognition times compared to other experimental groups **(#)** ($p<0.05$).

The mean memory time across the control and experimental groups as derived from the T-maze test is shown in Figure 3. The control group had significantly shorter memory times compared to co-codamol only, and co-codamol + curcumin groups (*****). However, the co-codamol only had significantly longer memory time compared to other experimental groups (**#**) ($p<0.05$).

TABLE 1: Body weights of control and experimental rats.

	Control	Cocodamol	Cocodamol+ Curcumin	Curcumin
Initial Weight (g)	262±6.782	264±4.082	261±3.742	261.3±9.465
Final Weight (g)	275±7.93	249.5±5.802	256.5±4.435	259.3±10.5
Weight Change (g)	13.25±5.852	-14.50±3.00	-4.50±1.291	-2.00±2.00
Weight Change (%)	5.06	-5.49	-1.72	-0.77

Values are expressed in mean ± SD of rats per group

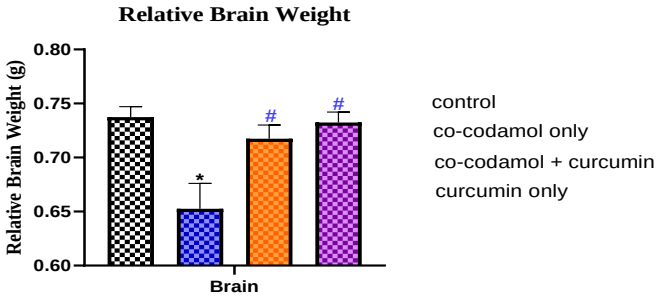

Figure 1: A bar chat of relative brain weight of control and experimental rats.

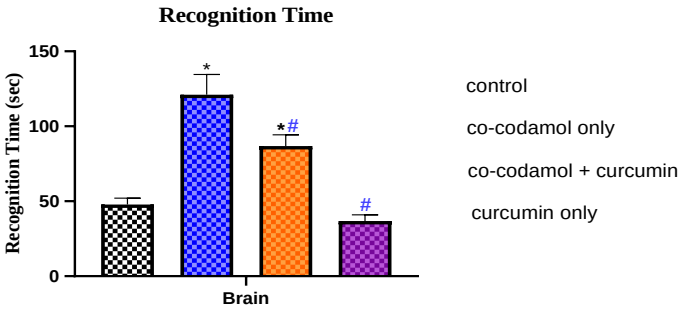

Figure 2: A bar chart of mean recognition time across the control and experimental groups as derived from the T-maze test.

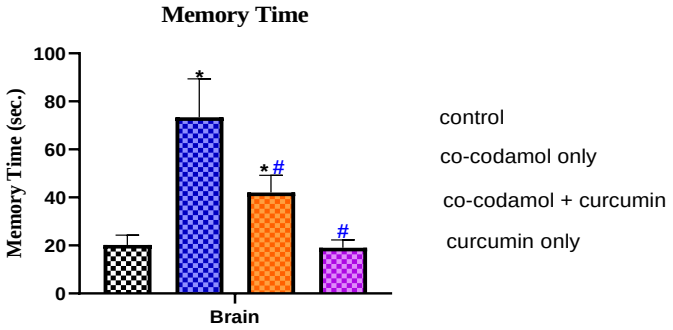

Figure 3: A bar chart of the mean memory time across the control and experimental groups as derived from the T-maze test.

DISCUSSION

The increasing use of pharmaceutical agents, particularly analgesics like co-codamol, raises concerns about their effects on brain health. Co-codamol, a combination of codeine and paracetamol, is widely prescribed for pain relief but has been linked to neurotoxicity, (Yang *et al.,* 2022; Adele *et al.,* 2022), this has led to a growing interest in finding substances that can mitigate this negative effect.

The current study assessed the effect of co-administration of co-codamol and curcumin on the brain of the adult male Wistar rats by analyzing the body and organs weights.

After administration, it was observed that rats in the control group were the most active while animals in co-codamol only group were observed to be the most senile and drowsy, with theu

slowest response to external stimuli which is similar with the studies of Achukwu *et al.,* (2019), who reported that the animals that received 15mg/kg of codeine were sluggish and restless compared to control which looked active and healthy. Hammed *et al.,* (2015), also observed that the rats administered with combination of codeine and paracetamol were drowsy compared to control.

A non-significant body weight loss was observed in the rats administered with co-codamol only and other groups (Figure 1). Achukwu *et al.,* (2019), reported a significant weight loss in rats that received 15mg/kg of codeine for five weeks compared to control rats, Philippot *et al.,* (2020) reported that there was no significant difference between the body weights of mice exposed to 60mg/kg of paracetamol and control, while the statistical analysis study of combination of codeine and paracetamol in animals' body weights done by Hameed *et al.,* (2015) showed a significant ($P \leq 0.05$) decrease especially in high dose treated group (160 mg of codeine/10000 mg of paracetamol/ kg b). The loss of weight observed could be due to a compromised nutritional status of the rats' consequent on gastrointestinal tract derangement, also the loss of appetite combined with drowsiness could be due to insufficient intake of opium (Hameed *et al.,* 2015; Fatemi *et al.,* 2008).

Furthermore, a significant decrease was seen in the relative brain weights of rats administered with co-codamol only compared to other groups which suggests neurotoxicity (Figure 2). Khaled *et al.,* (2024) reported a non-significant decrease in the relative brain weight of rabbits exposed to paracetamol.

Also, the significant increase seen in the relative brain weights of rats administered with curcumin only in this study, indicates the therapeutic potential of curcumin as a neuroprotective agent (Al-Askar *et al.,* 2017).

The rats that received coadministration of co-codamol and curcumin had improved body and brain weight loss compared to co-codamol only group possibly due to the neuroprotective effect of curcumin (Figure 1 and 2).

Curcumin treatment has been proven to be effective in promoting body and brain weight in valproic acid exposed pups (Al-Askar *et al.,* 2017), body and kidney weight of rats and mice with diabetic nephropathy (Wu *et al.,* 2014), and body and testicular weights of rats induced with chromium (Chandra *et al.,* 2007).

However, there is lack of study on the effect of co-administration of co-codamol and curcumin on the brain of adult Wistar rats.

In addition, this study evaluated the cognitive function of rats' post-administration using the T-maze test (Figure 3 and 4).

In this study, rats in control group had significantly shorter time to learn and remember the correct arm of the T-maze compared to co-codamol only group while the rats in co-codamol only group had significant decline in their ability to learn and remember the correct arm of the T-maze compared to rats administered with curcumin only and coadministration of co-codamol and curcumin groups. This suggests that curcumin improved learning ability and memory in these animals and repaired the cognitive dysfunction induced by co-codamol administration.

Previous studies reported that animals exposed to paracetamol displayed reduced memory, and learning ability compared to control (Viberg *et al.,* 2014; Blecharz-Klin *et al.,* 2018; Philippot *et al.,* 2020) while curcumin has been reported to provide protection against behavior deficits in fluid percussion injury of diabetic rats (Arun and Nalini, 2002; Wu *et al.,* 2014). A neuroprotective efficacy of curcumin in attenuating 3-nitropropionic acid (a fungal toxin) and lead induced neurotoxicity has been reported as well (Kumar *et al.,* 2007; Darian *et al.,* 2007).

Conclusion: This investigation provides evidence for co-codamol's detrimental influence on cognitive function in adult female Wistar rats, as reflected by their impaired performance in the T-maze test. Notably, co-administration with curcumin resulted in a significant improvement in cognitive outcomes, suggesting its neuroprotective effect against co-codamol-induced neurotoxicity. These findings underscore the promise of curcumin as a therapeutic strategy to mitigate cognitive decline associated with opioid use and warrant further exploration of its clinical utility as a complementary treatment approach. The study's results suggest that while taking co-codamol for pain management, curcumin could be taken along with it which could reduce or prevent the toxicity of co-codamol on the brain. Further studies using histology and biochemical analysis is encouraged.

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