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## NATURAL DRUGS

# CNS DEPRESSANT ACTIVITIES OF ROOTS OF *COCCOS NUCIFERA* IN MICE

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**Abstract:** The ethanol extract of *Coccos nucifera* (EECN) was tested for possible pharmacological effects on experimental animals. EECN significantly potentiated the sleeping time of mice induced by standard hypnotics *viz*. pentobarbital sodium, diazepam, and meprobamate in a dose dependent manner. EECN showed significant analgesic properties as evidenced by the significant reduction in the number of writhes and stretches induced in mice by 1.2 % acetic acid solution. It also potentiated analgesia induced by morphine and pethidine in mice. Pretreatment with EECN caused significant protection against pentylenetetrazole-induced convulsions. The behavioral studies on mice indicate CNS depressant activity of the ethanol extract of *C. nucifera*.

**Keywords:** *Coccos nucifera*, sleeping time, general behavior, analgesic activity, anticonvulsant activity

*Coccos nucifera* (Nariyal in Hindi; Narikel, Dab in Bengali; Nadia, Paida in Oriya, family: Palmae) is a tall tree distributed throughout tropical islands, coasts, Southern India, South America, Florida, Bahamas in North America and Ceylon. Every part of the coconut palm is used by man. Seeds are cooling, tonic, laxative, cardiotonic and useful in the treatment of leprosy, tuberculosis, liver complaints, piles, etc. (1). Bark is good for teeth and scables. Flower is useful in diabetes, dysentery, urinary discharges (2, 3). Root is diuretic, astringent, anthelmintic, antioxidant used in uterine diseases (4).

The ethanol extract of *C. nucifera* (EECN) showed marked CNS depressant action compared to other extracts of it in preliminary pharmacological screening. However, no work has been reported on the CNS activities of this plant. Keeping this in view, the present study has been undertaken to investigate various CNS activities such as behavioral, sedative-hypnotic, analgesic, and anticonvulsant effects of EECN in mice to substantiate the folklore claim.

## EXPERIMENTAL

### Plant material

Fresh roots of *C. nucifera* L. were collected from the district of Hooghly, West Bengal, India in the month of September and were authenticated by Dr H. J. Chowdhury, Joint Director, Central National Herbarium, Botanical Survey of India, Howrah, West Bengal. A voucher specimen has been preserved in our laboratory for future reference (DAS 1).

### Extraction

Shade-dried, powdered, sieved (40 mesh size) plant material was exhaustively extracted successively with petroleum ether (40–60$^{o}$C), chloroform, ethanol and distilled water using a Soxhlet extractor. The extracts were concentrated to dryness in vacuum. The yield of ethanol extract (EECN) was 10.7 % w/w.

### Chemical investigation of EECN

The ethanol extract of root of *C. nucifera* (EECN) on preliminary chemical analysis was found to contain polyphenols, saponins and flavonoids (5, 6).

EECN was subjected to silica gel preparative TLC, where one compound was isolated using acetone : ethanol : petroleum ether: glacial acetic acid (1 : 2.5 : 1 : 1 drop) as solvent system. Compound A ($R_f$ value: 0.6, $\lambda_{max}$: 256 nm) having characteristic IR (Perkin Elmer, IR-297) peaks at 3411.46, 2929.34, 2139.63, 1417.42, 1642.09, 1561.09 and

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1019.19 $cm^{-1}$ suggested the structural similarities with the polyphenolic type of compounds (7).

**Experimental animals**

Adult Swiss albino mice of either sex (22 ± 2 g) obtained from B.N. Ghosh & Co., Kolkata were acclimatized to normal laboratory conditions for one week and given pellet diet (Hindustan Lever Ltd., India) and water *ad libitum*. All experiments were performed between 8 a.m. to 12 p.m. to minimize circadian influences. The experimental protocol was subjected to the scrutiny of the Institutional Animal Ethical Committee and was cleared before starting. The animals were handled as per guidelines of committee for the purpose of control and supervision on experimental animals (CPCSEA), New Delhi. For the pharmacological testing, the ethanol extract of C. *nucifera* (EECN) was dried completely. The trace amount of ethanol which might be present within the solid mass of extract was removed under vacuum. Then EECN was dissolved in propylene glycol.

**Pharmacological studies**

Safety evaluation

An acute toxicity study relating to the determination of the $LD_{50}$ value was performed with different doses of EECN into different group of mice, each containing 10 animals, as per the method described by Litchfield and Wilcoxon (8).

Barbiturate potentiation

Mice were divided into 4 groups, each group containing 6 mice. The animals of group I served as the vehicle control (propylene glycol, 5 mL/kg); groups II, III, and IV received EECN at a low, medium and high dose (40 mg/kg, 60 mg/kg and 80 mg/kg, respectively). Vehicle control and the extracts were injected intraperitoneally 30 min prior to the administration of pentobarbital sodium (40 mg/kg, *i.p.*), diazepam (3 mg/kg, *i.p.*) and meprobamate (100 mg/kg, *i.p.*). The sleeping time was noted by recording the interval between the losses and regaining of righting reflex (9, 10).

Analgesic activity

The analgesic activity was tested by the following methods:

(i) Acetic acid-induced writhing (chemical stimulus) method

This method, involved intraperitoneal injection of freshly prepared 1.2% v/v acetic acid. The number of abdominal constrictions (writhing) and stretching with a jerk at the hind limbs and bending of trunk were counted between 5 and 15 min after administration of acetic acid (11–14). The analgesic effect of the drugs was calculated by the percentage inhibition of writhing episode over that of the control group. The results were compared with those of acetylsalicylic acid (ASA) (68 mg/kg), paracetamol (PCM) (68 mg/kg) and morphine sulfate (M) (1.15 mg/kg).

ii) Thermal stimulus by Eddys hot plate method

The analgesic actions were studied using Eddys hot plate method (15). The reaction time was taken as the interval extending from the instant the mouse reached the hot plate till the animal licked its feet or jumped out of the cylinder. The reaction time was recorded at 30, 45, 60, 90, 120, 150, and 180 min after intraperitoneal injection of EECN at doses of 40, 60, and 80 mg/kg. The temperature of the hot plate was maintained at 55 ± 0.5°C. A cut off reaction time of 30 s was chosen in order to avoid the physical injury. Morphine and pethidine were used as a reference drugs at doses of 5 and 10 mg/kg, *i.p.*, respectively. EECN was given individually and also 15 min prior to the administration of reference drugs to investigate the potentiation of morphine and pethidine activity (16, 17).

Anticonvulsant activity

EECN was administered in varying doses (25–80 mg/kg, *i.p.*) 30 min prior to the administration of pentylenetetrazole (80 mg/kg, *i.p.*). One group received vehicle (propylene glycol, 5 mL/kg, *i.p.*), and another group received diazepam (2.0 mg/kg, *i.p.*) as a reference standard. The onset and incidence of clonic convulsions were observed. Also, nature and severity of convulsions and the percentage of mortality after 24 h were recorded. Each group contained six animals (17–20).

Behavioral effects

The effects of EECN (40, 60, and 80 mg/kg, *i.p.*) on righting reflex, pinna reflex, corneal reflex, awareness, grip strength, touch and pain responses on mice were observed by conventional methods. Chlorpromazine (5 mg/kg, *i.p.*) was used as a reference drug (21–23).

**Statistical analysis**

Results are expressed as the mean ± SEM. ANOVA followed by Dunnett's't' test was performed as a *post hoc* test of significance taking vehicle treated animals as control; p value of $< 0.05$ was considered as statistically significant.

Table 1. Effect of EECN on sleeping time (min) induced by pentobarbitone, diazepam, and meprobamate in mice.

| Treatment | Sleeping time (min) induced by | | |
|---|---|---|---|
| | Pentobarbital (40 mg/kg, *i.p.*) | Meprobamate (100 mg/kg, *i.p.*) | Diazepam (3 mg/kg, *i.p.*) |
| Control (PG, 5 mL/kg, *i.p.*) | 40.3 ± 0.91 | 61.6 ± 0.90 | 74.9 ± 0.87 |
| EECN(40 mg/kg, *i.p.*) | 78.3 ± 2.05[a] | 93.6 ± 1.95[a] | 136.7 ± 2.04[a] |
| EECN(60 mg/kg, *i.p.*) | 95.6 ± 2.14[a] | 112.0 ± 2.00[a] | 193.5 ± 3.20[a] |
| EECN(80 mg/kg, *i.p.*) | 115.7 ± 2.20[a] | 128.5 ± 3.02[a] | 232.1 ± 3.70[a] |

Values are the mean ± SEM from 6 animals in each group. Statistical analysis done by ANOVA followed by *post hoc* test of significance, Dunnett's 't' test. [a]$p < 0.001$ *vs*. vehicle control. PG: propylene glycol, *i.p.*: intraperitoneal.

Table 3. Anticonvulsant effect of EECN on pentylenetetrazole (PTZ)-induced convulsions in mice.

| Treatment | Onset of clonic convulsion (in s) | Incidence of convulsions (%) | Nature and severity | Death / Recovery |
|---|---|---|---|---|
| Control (PG, 5 mL/kg, *i.p.*) | 70.4 ± 3.6 | 100 | Major jerking | All died |
| EECN (25 mg/kg, *i.p.*) | 242.6 ± 8.8* | 60.7 | Minor jerking | 60.7 % died |
| EECN (40 mg/kg, *i.p.*) | 307.9 ± 10.9* | 44.2 | Minor jerking | 44.2 % died |
| EECN (60 mg/kg, *i.p.*) | 410.6 ± 14.7* | 29 | Minor jerking | No death |
| EECN (80 mg/kg, *i.p.*) | A | 0 | Nil | No death |
| Diazepam (2 mg/kg, *i.p.*) | A | 0 | Nil | No death |

Values are the mean ± SEM. Statistical analysis done by ANOVA followed by *post hoc* test of significance, Dunnett's 't' test. *$p < 0.05$ *vs*. vehicle control. PG: propylene glycol, *i.p.*: intraperitoneal, n = 6, A = absence of convulsions.

## RESULTS

Safety evaluation

Acute toxicity tests in mice established the $LD_{50}$ of EECN to be 400 mg/kg, *i.p.*

Barbiturate potentiation

Three doses of EECN (40, 60, and 80 mg/kg) potentiated the sleeping time induced by standard hypnotics *viz*. pentobarbital (94.3%, 137.2%, and 187.1%, respectively), diazepam (82.5%, 158.3%, and 209.9%, respectively) and meprobamate (51.9%, 81.8%, and 108.6%, respectively) (Table 1).

**Analgesic activity**

EECN exhibited a dose dependent and remarkable analgesic activity in the acetic acid induced writhing test. As can be seen in Figure 1, EECN with a dose of 40 mg/kg, *i.p.* exhibited percentage of protection 65%. This dose dependent effect reached 100% with a dose of 80 mg/kg, *i.p.* Analgesic compounds: acetylsalicylic acid (68 mg/kg, *i.p.*), morphine sulfate (1.15 mg/kg, *i.p.*), and paracetamol (68 mg/kg, *i.p.*) gave 60%, 70%, and 61% protection, respectively. From Table 2, it can be seen that EECN not only produced analgesia in mice but also potentiated the analgesic action of morphine and pethidine.

Anticonvulsant activity

In pentylenetetrazole-induced seizures, in the animals treated with vehicle, clonic convulsion appeared 70.4 ± 3.6 s after PTZ administration and all animals died after seizures. EECN significantly and dose dependently inhibited the onset and incidence of convulsions. The convulsions were completely abolished by the dose of 80 mg/kg, *i.p.* EECN in a dose of 25 mg/kg, *i.p.* exhibited seizures in 60.7% of mice and all animals exhibiting seizures died within 30 min. No mortality was observed in the groups treated with EECN at 70 and 80 mg/kg, *i.p.* even after 24 h. Diazepam (2 mg/kg, *i.p.*) inhibited seizures completely (Table 3).

Effect on general behavioral profiles

The results obtained from general behavioral profiles are shown in Table 4. It was noted that

Table 2. Effect of EECN on analgesia induced by morphine and pethidine in mice (by hot plate method).

| Treatment | Resting value | Average maximum reaction time (s) at min | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 15 | 30 | 45 | 60 | 90 | 120 | 150 | 180 |
| Control (PG, 5 mL/kg, *i.p.*) | 4.8 ± 0.06 | 10.1± 1.23 | 7.6 ± 0.05 | 5.3 ± 0.03 | 5.1 ± 1.09 | 4.2 ± 1.02 | 4.1 ± 0.72 | 3.7 ± 1.01 | 3.1 ± 0.32 |
| EECN (40 mg/kg, *i.p.*) | 4.9 ± 0.79 | - | 20.7 ± 1.00[a] | 16.3 ± 1.16[a] | 13.2 ± 0.9[a] | 11.5 ± 0.83[a] | 8.0 ± 0.04 | 7.0 ± 0.70 | 6.5 ± 0.64 |
| EECN (60 mg/kg, *i.p.*) | 5.1 ± 0.92 | 28.3 ± 1.05[a] | 25.6 ± 1.30[a] | 19.4 ±1.09[a] | 16.2 ± 1.23[a] | 14.8 ± 1.35[a] | 11.0 ± 0.96[a] | 8.5 ± 0.82 | 7.2 ± 0.70 |
| EECN (80 mg/kg, *i.p.*) | 4.6 ± 0.08 | >30[a] | >30[a] | >30[a] | >30[a] | >30[a] | >30[a] | 20.2 ±0.80[a] | 14.1 ± 1.12[a] |
| Morphine (5 mg/kg, *i.p.*) | 5.6 ± 0.91 | >30[a] | 19.3 ± 0.42[a] | 18.6 ± 1.04[a] | 14.4 ± 0.94[a] | 9.9 ± 1.18[a] | 8.1 ± 0.82[a] | 6.5 ± 0.72 | 5.0 ±0.34 |
| EECN (40 mg/kg, *i.p.*) + Morphine | 5.3 ± 0.87 | >30[a] | >30[a] | 29.6 ± 1.49[a] | 26.6 ± 0.80[a] | 23.2 ± 0.95[a] | 14.2 ± 1.30[a] | 11.2 ± 0.86[a] | 8.7 ± 0.80 |
| EECN (60 mg/kg, *i.p.*) + Morphine | 5.9 ± 0.62 | >30[a] | >30[a] | >30[a] | >30[a] | 26.3 ± 1.71[a] | 17.9 ± 2.61[a] | 13.6 ± 1.23[a] | 12.1 ± 0.25[a] |
| EECN (80 mg/kg, *i.p*) + Morphine | 5.9 ± 0.94 | >30[a] | >30[a] | >30[a] | >30[a] | >30[a] | >30[a] | >30[a] | 22.9 ± 1.82[a] |
| Pethidine (10 mg/kg, *i.p.*) | 5.0 ± 0.83 | 25.2 ± 1.27[a] | 23.1 ± 1.39[a] | 15.6 ± 0.52[a] | 11.4 ± 1.05[a] | 9.5 ± 0.91[a] | 6.1 ± 0.91[a] | 4.4 ± 0.94 | 3.9 ± 0.80 |
| EECN (40 mg/kg, *i.p*) + Pethidine | 5.7 ± 0.78 | 28.5 ± 1.00[a] | 27.5 ± 1.22[a] | 20.8 ± 1.97[a] | 18.1 ± 1.28[a] | 17.0 ± 1.39[a] | 12.6 ± 1.70[a] | 10.3 ± 0.94[a] | 8.2 ± 0.71 |
| EECN (60 mg/kg, *i.p.*) + Pethidine | 5.6 ± 1.10 | >30[a] | >30[a] | >30[a] | 23.4 ± 1.07[a] | 19.5 ± 1.58[a] | 16.4 ± 1.18[a] | 13.8 ± 1.12[a] | 11.2 ± 0.70[a] |
| EECN (80 mg/kg, *i.p*) + Pethidine | 5.8 ± 0.94 | >30[a] | >30[a] | >30[a] | >30[a] | >30[a] | >30[a] | >30[a] | 22.6 ± 1.23[a] |

Values are the mean ± SEM from 6 animals in each group. Statistical analysis done by ANOVA followed by *post hoc* test of significance, Dunnett's 't' test, [a] $p < 0.05$ *vs*. resting value (average reaction time before treatment). Results of (EECN + morphine) and (EECN + pethidine) were significant ($p < 0.05$) *vs*. EECN. PG: propylene glycol; >30: animals fail to react within 30 s (30 s response latency); *i.p.*: intraperitoneal.

Table 4. Effect of EECN on behavioral profiles in mice.

| Treatment | Awareness Response | Touch response | Pain response | Righting reflex | Pinna reflex | Corneal reflex | Grip strength |
|---|---|---|---|---|---|---|---|
| Control (PG, 5 mL/kg, *i.p.*) | 0 | 0 | 0 | 0 | 0 | 0 | + |
| Chlorpromazine (5 mg/kg, *i.p.*) | 4+ | 4+ | 4+ | 4+ | 4+ | 4+ | 4+ |
| EECN (40 mg/kg, *i.p.*) | 2+ | 3+ | 3+ | 2+ | 2+ | 3+ | 2+ |
| EECN (60 mg/kg, *i.p.*) | 3+ | 4+ | 4+ | 3+ | 3+ | 4+ | 3+ |
| EECN (80 mg/kg, *i.p.*) | 4+ | 4+ | 4+ | 4+ | 4+ | 4+ | 4+ |

Key for scoring: 0: no effect (normal); +: slight depression; 2+: moderate depression; 3+: strong depression; 4+: very strong depression. *i.p.*: intraperitoneal. PG: propylene glycol. Number of animals used for each group (n = 6).

EECN depressed awareness and alertness, touch and pain responses, grip strength, altered righting, pinna and corneal reflexes when compared to the control (propylene glycol, 5 mL/kg). However, chlorpromazine hydrochloride (standard) produced a significant depression of these responses in comparison with EECN.

## DISCUSSION AND CONCLUSION

Pentobarbital, diazepam and meprobamate were used to induce sleep in this study. Benzodiazepines are believed to act at specific binding sites that are closely linked to γ-aminobutyric acid (GABA) receptors, the binding of benzodiazepines enhancing GABA-ergic transmission. Although the cause of prolongation of diazepam-induced sleeping time is not known, the enhancement of GABA-ergic transmission might be related to its sedative activity. Prolongation of pentobarbital induced sleeping time might be due to tranquilizing action as well as CNS depressant action. Although the exact mechanism responsible for the sedation action of meprobamate is not clear, it might be due to CNS depressant action or due to enhancement of GABA-ergic transmission (12, 16, 17, 24). EECN potentiated significantly the duration of pentobarbital, diazepam and meprobamate–induced sleep in mice, suggesting probable tranquilizing action as well as CNS depressant action (13, 22).

Pal et al. found that analgesic activity of *Celsia coromandeliane* is probably mediated by inhibition of a post synaptic specific sensitive mechanism either by depleting endogenous levels of nor-epinephrine *via* dopamine-β-hydroxylase inhibition or by blocking norepinephrine effects at the receptor level (25). Analgesic and anticonvulsant activities can also be mediated by other mechanisms. The increase of brain serotonin and GABA level is responsible for analgesic and anticonvulsant activities (16, 17, 20, 25–27). It was found that EECN increased the brain serotonin and GABA level in mice (unpublished data). Therefore, profound analgesic and anticonvulsant activities produced by EECN may be related to the increased brain serotonin and GABA level in mice (25).

Gupta et al. established that inhibition of the touch response, righting reflex, and grip strength is probably produced due to a pronounced CNS depressant action (19). Reduction of pinna reflex and awareness may be due to synapses block of the afferent pathway or due to overall CNS depressant action (28, 29). In this study, the mechanism whereby EECN depressed awareness, touch and pain responses, righting reflex, pinna reflex, corneal reflex, and grip strength may also be due to synapses block of the efferent pathway or by overall CNS depressant action (30).

The exact chemical components responsible for such CNS depressant activity of EECN are not known. Preliminary phytochemical studies revealed that it contain saponin which might be responsible for anticonvulsant properties of EECN (25, 26).

EECN enhanced sleeping time, analgesic, and anticonvulsant activities and reduced different behavioral reflexes. It can be concluded from the present discussion that the ethanol extract of *C. nucifera* exhibited strong CNS depressant action.

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