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Original Article

# Evaluation of Analgesic and Antipyretic Effects of Ethanolic Extract of *Helianthus annuus* Seeds in Wistar Albino Rats

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## ABSTRACT

**Introduction:** Pain is a complex, multifactorial sensory and emotional experience that serves as a protective physiological mechanism but may become pathological when persistent. Pain and fever have an overlapping inflammatory mechanism. NSAIDs are commonly used for the treatment of both conditions but these agents are associated with several adverse effects. *Helianthus annuus L.* (sunflower), a member of family Asteraceae, is widely cultivated throughout the world and is valued not only for its nutritional importance but also for its medicinal properties. No previous research has been performed to assess analgesic and antipyretic properties of *Helianthus annuus* seed extract; therefore, the present study aims to evaluate these effects using established experimental animal models. **Materials and Methods:** The study was done in department of pharmacology after receiving IAEC (Institutional Animal Ethics Committee) approval for a period of 30 days. The rats were divided in four groups containing 6 rats each. The study was conducted in two sequential phases using the same set of animals. In the first phase, analgesic activity was evaluated. After completion of the analgesic experiments, a washout period of one week was allowed. The same animals were then used in the second phase for evaluation of antipyretic activity. **Results:** All the values are expressed as Mean±SD. Significant reduction in pain perception and temperature was seen after giving the extract, where the highest dose of extract did maximum reduction which is comparable to the standard drug. **Conclusion:** Our study concludes that *Helianthus annuus* seed extract may be a valuable natural source of bioactive compounds exhibiting analgesic and antipyretic effects.

**Keywords:** Acetic acid writhing, Analgesiometer, Brewer's yeast test, *Helianthus annuus*, Pain, Pyrexia.

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## INTRODUCTION

Pain is a complex, multifactorial sensory and emotional experience that serves as a protective physiological mechanism but may become pathological when persistent. Chronic pain, defined as pain lasting longer than 3 months, is a major global health problem and one of the major causes of disability worldwide (Zhang *et al.*, 2025). Estimates based on the Global Burden of Diseases (GBD) 2021 study suggest that chronic pain affects populations across 204 countries and territories, commonly due to musculoskeletal disorders, arthritis as well as cancer and it is not evenly distributed i.e., it varies by age and gender (Goyal & Mohanty, 2024). Studies in India have reported that nearly half of adults aged ≥ 45 years do experience joint pain, while approximately one-third suffer from chronic back pain, ankle, or foot pain (Zhang *et al.*, 2025; Goyal & Mohanty, 2024).

Pain and fever have an overlapping inflammatory mechanism. Tissue injury or infection activates phospholipase $A_2$, causing the release of arachidonic acid from membrane phospholipids. This substrate is subsequently metabolized by Cyclooxygenase (COX) enzymes into prostaglandins, particularly Prostaglandin $E_2$ ($PGE_2$), which have an important role in nociception and thermoregulation. Increased expression of COX-2(Cyclooxygenase-2) leads to elevated prostaglandin production, lowering the pain threshold and contributing to inflammatory hyperalgesia. Therefore, inhibition of prostaglandin synthesis remains a principal target in pain management. "NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)", including paracetamol, are broadly employed pharmacological agents for management of pain and fever. NSAIDs exert their effects primarily through inhibition of "COX-1(Cyclooxygenase-1) and /or COX-2 (Cyclooxygenase-2) enzymes," thereby reducing prostaglandin synthesis (Ahmadi *et al.*, 2022; Charde *et al.*, 2025). This clinical use of these agents often causes significant

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adverse effects. Common complications include gastric irritation, dry mouth, peptic ulcer disease, bleeding, renal impairment, and increased cardiovascular risk. COX-1(Cyclooxygenase-1) inhibition compromises gastric mucosal protection, while prostaglandin suppression may predispose individuals to acute kidney injury (Charde *et al.*, 2025). Paracetamol, while safer for gastrointestinal and renal systems than NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), risks hepatotoxicity when taken in excessive doses or with depleted glutathione reserves.

In this context, plant-derived therapies have increasingly been explored as a possible alternative to safer analgesic and anti-inflammatory agents. Herbal medicines have been used traditionally across many cultures for symptomatic treatment of "pain and inflammatory conditions," as well as growing scientific evidence supports their pharmacological potential (Suciu *et al.*, 2025). *Helianthus annuus* L. (sunflower), a member of family Asteraceae, is widely cultivated throughout the world and is valued not only for its nutritional importance but also for its medicinal properties. Sunflower seeds contain various bioactive compounds, including flavonoids, alkaloids, terpenoids, steroids, and phenolic constituents (Islam *et al.*, 2016). Previous phytochemical studies of *Helianthus annuus* seeds have confirmed the presence of these compounds, many of which are known to possess anti-inflammatory and analgesic activities. Flavonoids, for example, have been reported to modulate prostaglandin synthesis and suppress inflammatory signalling pathways, while alkaloids may influence nociceptive transmission and central pain modulation mechanisms (Islam *et al.*, 2016).

The rising global burden of chronic pain, along with the adverse effects of conventional pharmacotherapies, highlights the imperative to explore safer and more effective treatment alternatives. Natural substances demonstrating established antioxidant and anti-inflammatory characteristics, along with initial evidence of analgesic efficacy in animal models, indicate the compelling opportunities for additional pharmacological investigation. No previous research has been performed to assess analgesic and antipyretic properties of *Helianthus annuus* seed extract; therefore, the present study aims to evaluate these effects using established experimental animal models. The findings of this research may provide experimental support for therapeutic potential of sunflower seeds and help in identifying a possible plant-based source of safer analgesic and antipyretic agents.

## MATERIALS AND METHODS

### Design and setting

In the pharmacology department of "Kalinga Institute of Medical Sciences (KIMS), KIIT University," Bhubaneswar, Odisha, India, a prospective controlled animal study was carried out at the Animal House Facility. Prior to the experiment, the study protocol was reviewed and approved by the Institutional Animal Ethics Committee (IAEC).

CCSEA (Committee for control and supervision of experiment on animals) guidelines for the use and care of laboratory animals were followed in planning and execution of all experimental procedures. Additionally, the study addressed the three Rs: replacement, reduction, and refinement. The total duration of the study was for thirty days.

### Experimental animals

This study used 24 adult male Albino Wistar rats in healthy condition, weighing 150 to 200 grams and aged two to three months. To ensure uniformity and prevent any hormonal variations, male rats were selected. The animals were obtained from CCSEA (Committee for control and supervision of experiment on animals)-approved sources and were housed in the animal house facility, KIMS (Kalinga Institute of Medical Science), Bhubaneswar, under standard laboratory conditions. They had unrestricted access to water ad libitum and standard diet while being kept in sterile cages in controlled environments. Before the experiment started, the animals were thoroughly adjusted to laboratory environment. Standard care was taken throughout the study to minimize stress and discomfort.

### Preparation of plant extract

The seeds of *Helianthus annuus* were dried, powdered, and subjected to ethanolic extraction using 95% ethanol by cold maceration process (shown in Figure 1). The obtained extract was concentrated and preserved appropriately until use. Fresh preparation of the extract suspension was made before oral administration to the animals. The ethanolic extract of *Helianthus annuus* seeds was used as the test drug in the study.

### Drugs and chemicals

The test drug that was used in the study was an ethanolic extract of *Helianthus annuus* seeds administered orally at two graduated dose levels, 100 mg/kg and 200 mg/kg. Pethidine, administered intraperitoneally at dose of 5 mg/kg, has been standard drug used to assess analgesic activity. Paracetamol, administered orally at dose of 150 mg/kg, has been standard drug used to assess antipyretic activity. Normal saline employed in control treatment group. Acetic acid was used as a chemical for induction of pain, and 20% brewer's yeast suspension was used for induction of pyrexia.

### Experimental design and grouping

The study was conducted in two sequential phases using the same set of animals. In the first phase, analgesic activity was evaluated. After completion of the analgesic experiments, a washout period of one week was allowed. The same animals were then used in the second phase for evaluation of antipyretic activity.

Animals were divided into 4 groups of 6 rats each for the analgesic phase:

**Group I:** Control group receiving normal saline,

**Group II:** Standard group receiving pethidine 5 mg/kg intraperitoneally,

**Group III:** Test group receiving ethanolic extract of *Helianthus annuus* seeds 100 mg/kg orally,

**Group IV:** Test group receiving ethanolic extract of *Helianthus annuus* seeds 200 mg/kg orally.

After a washout period of one week, the same animals were used for the antipyretic phase and again evaluated in four groups:

**Group I:** Control group receiving normal saline,

**Group II:** Standard group receiving paracetamol 150 mg/kg orally,

**Group III:** Test group receiving ethanolic extract of *Helianthus annuus* seeds 100 mg/kg orally,

**Group IV:** Test group receiving ethanolic extract of *Helianthus annuus* seeds 200 mg/kg orally.

## Evaluation of analgesic activity

### *Tail-flick method*

The "tail-flick method" has been used to determine central analgesic activity in rats using an analgesiometer. Baseline reaction time was recorded before administration of drugs. Following the treatment (standard and test drugs), tail-flick latency was measured at 0, 30, 60, 90, and 120 min. To prevent any tissue injury, cut-off time of 10 sec has been maintained. Prolongation of reaction time was considered indicative of analgesic activity. Pethidine was used as the standard analgesic drug in this model.

## Acetic acid-induced writhing method

It has been utilized to assess peripheral analgesic activity. Writhing pain is a type of severe, twisting discomfort that causes an involuntary, contorted response from the body. Intraperitoneal administration of 10 mL/kg of 0.6% acetic acid caused this phenomenon. Following treatment, animals were monitored and writhes counted for 20 min. Analgesic activity was determined by comparing number of writhes to that of the control group. Standard drug was 5 mg/kg of pethidine administered intraperitoneally.

## Washout period

On completion of the analgesic phase, a washout period of one week was given before commencement of the antipyretic phase, in order to minimize carryover effect of the previously administered drugs. The same set of animals was then used for antipyretic evaluation.

## Evaluation of antipyretic activity

The "Brewer's Yeast-induced Pyrexia model" has been utilized to determine antipyretic activity. A subcutaneous injection of 20% brewer's yeast suspension at a dose of 20 mL/kg below nape of the neck was used to induce fever. After 18 to 20 hr, the rectal temperature was measured to verify pyrexia. The standard and test drugs were then administered orally. Rectal temperature was subsequently recorded at 24 hr post-injection, then 30, 60, 90 and 120 min. Reduction in elevated rectal temperature compared with



1a



1b

**Figure 1:** Shows the process of extraction of ethanolic extract of *Helianthus annuus* seeds by cold maceration process.

**Table 1: Analgesic activity of the extract in rats using tail flick method (analgesiometer).**

| Groups | Treatment | Dose | Reaction time after administration of drug (in seconds) | | | | |
|---|---|---|---|---|---|---|---|
| | | | Basal | 30 mins | 60 mins | 90 mins | 120 mins |
| I | Control | NS (NORMAL SALINE) 1 mL | 9.1±0.67 | 9.44±1.71 | 9.53±0.42 | 10.02±0.71 | 10.17±0.73 |
| II | Standard | 5 mg/kg | 11.67±0.66* | 15.45±0.41** | 19.5±0.34**& | 20.12±0.32**& | 22.31±0.61**& |
| III | Extract | 100 mg/kg | 10.21±0.72 | 12.07±0.56* | 15.22±0.84**& | 17.54±0.65**& | 18.32±0.55**& |
| IV | Extract | 200 mg/kg | 10.52±0.87 | 13.22±0.44* | 17.25±0.75**& | 19.34±1.28**& | 21.23±0.78**& |

All values expressed as Mean±SD (Standard Deviation). "One-way ANOVA (Analysis of Variance" and "Tukey's *post hoc* test" have been employed to compare groups. When compared to control group, *indicates $p<0.05$ (significant) and **$p<0.001$ (very significant), whereas &demonstrates that all three groups (II, III, and IV) are equivalent at 60, 90, and 120 min.

**Table 2: Analgesic activity of the extract in rats using acetic acid writhing method.**

| Group | Treatment | Dose | Number of Writhing Observed (20mins) | % inhibition |
|---|---|---|---|---|
| I | Control | NS (NORMAL SALINE) 1 mL | 31.27±1.76 | - |
| II | Standard | 5 mg/kg | 12.55±0.56**& | 61.35% |
| III | Extract | 100 mg/kg | 20.15±0.87* | 33.54% |
| IV | Extract | 200 mg/kg | 17.23±0.45**& | 53.71% |

Mean±SD is used to express all values. The Tukey's *post hoc* test was used after the one-way ANOVA (Analysis of variance) to compare the groups. When compared to control group, *indicates $p<0.05$ (significant) and **$p<0.001$ (highly significant), whereas &signifies comparability of two groups (II and IV).

**Table 3: Antipyretic activity of extract in rats at different time intervals.**

| Groups | Treatment | Dose | Rectal temperature (°F) after administration of drug | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Basal | 24 hr post yeast injection | 30 min | 60 min | 90 min | 120 min |
| I | Control | NS (NORMAL SALINE) 1 mL | 94.53±0.39 | 99.88±0.38 | 100.21±0.14 | 100.52± 0.35 | 100.85±0.39 | 101.12±0.45 |
| II | Standard | 150 mg/kg | 94.45±0.36 | 99.75±1.31 | 97.65±0.36* | 96.5±0.39* | 94.87±0.78**& | 94.43±0.53**& |
| III | Extract | 100 mg/kg | 94.76±0.44 | 100.05±0.55 | 97.6±0.32* | 96.1± 0.51* | 95.9±0.78* | 94.15±0.81**& |
| IV | Extract | 200 mg/kg | 94.35±0.64 | 100.02±1.08 | 96.9±0.35* | 96.54± 0.76* | 94.65±0.45**& | 94.34±0.54**& |

All values expressed as Mean±SD. "One-way ANOVA (Analysis of Variance)" and "Tukey's *post hoc* test" have been utilized to compare groups. *Indicates $p<0.05$ (significant) and **$p<0.001$ (highly significant) when compared with control group while &indicates that all three groups (II, III, IV) are comparable at 120 min.

the control group was taken as evidence of antipyretic activity. Paracetamol served as the standard drug in this phase.

All procedures were carried out by trained and experienced personnel and no survival surgery was performed. The study did not include blood withdrawal, radiation exposure, or euthanasia as part of the experimental procedure. Animals were monitored during the course of the study for signs of stress or discomfort, and post-experimental reuse/rehabilitation within the animal house facility was carried out as per institutional policy.

## Statistical analysis

Mean±Standard Deviation (SD) is employed to express all data. "One-Way Analysis of Variance (ANOVA)" and "Tukey's *post hoc* test" for multiple intergroup comparisons are statistical tests utilized for analysis. $p$ value is <0.05(statistically significant).

# RESULTS

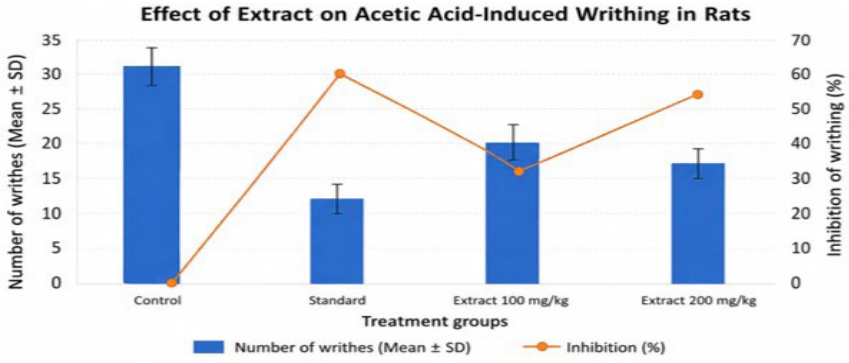



**Figure 2:** Effect of ethanolic extract of *Helianthus annuus* seeds on acetic acid-induced writhing in rats. Bars represent the mean number of writhes with error bars, and the line represents percentage inhibition of writhing.

## DISCUSSION

Pain and fever are closely linked to the inflammatory pathways, particularly by prostaglandin, such as prostaglandin E2, which plays an important role in nociception and thermoregulation. Various harmful stimuli that cause pain are usually mechanical, chemical, or thermal in nature. These stimuli activate the peripheral nerve endings of specialized sensory neurons that supply different tissues, with their cell bodies located in the dorsal root and trigeminal ganglia. These pain-detecting nerve fibers are known as nociceptors. When their nerve endings are stimulated, they become depolarized, triggering action potentials that travel to the dorsal root ganglia (DRG), leading to the sensation of pain (Malfait *et al.*, 2021). Analgesic medications such as morphine act centrally by increasing the pain stimulus threshold, whereas drugs such as aspirin and other NSAIDs have a peripheral effect by preventing the production and action of "inflammatory molecules" (Ahmadi *et al.*, 2022). Antipyretic medications, including paracetamol, typically reduce fever by inhibiting the hypothalamus from producing prostaglandins in response to internal or external signals that induce fever (Charde *et al.*, 2025). The ethanolic extract of *Helianthus annuus* seeds demonstrated dose-dependent pattern of significant analgesic and antipyretic action in Wistar albino rats in the current research.

Table 1 shows that the ethanolic extract of *Helianthus annuus* seeds causes prolongation of reaction time in tail-flick test in both doses of test drug (100 mg/kg, 200 mg/kg), but greater effect was seen at 200 mg/kg. The response became significant after 30 min and was highly significant after 60, 90, and 120 min. The higher dosage of the test drug demonstrated efficacy nearly equivalent to the standard medication. Tail-flick test is usually considered a measure of central mediation of antinociceptive effectiveness. Findings of this study suggested that extract may possess a primary antinociceptive action. The gradual increase in delay over time indicated that the drug's effect is prolonged rather than transient. The results of the present study corroborate with previous research conducted by Islam *et al.* In their work, "methanolic extract" of *Helianthus annuus* seeds showed significant antinociceptive effectiveness in experimental mice (Islam *et al.*, 2016). The present study also supports the fact that *Helianthus annuus* has analgesic activity, though there are no similar studies supporting our evidence.

Table 2 depicts significant reduction in the incidence of writhing after administration of standard and test drugs. The extract decreased number of writhes by 33.54% at 100 mg/kg and by 53.71% at 200 mg/kg (Figure 2). Therefore, percentage inhibition of writhes of the higher dose of the test drug is comparable to the standard drug (61.35%). An established experimental model for assessing peripheral analgesic activity is acetic acid-induced writhing test. "Nociceptive response" produced by acetic acid is primarily attributed to the release of endogenous pain mediators, particularly prostaglandins (Deraedt *et al.*, 1980). Therefore, inhibition of writhing in this model suggests a significant suppression of peripheral inflammatory pain pathways. The results of this research show that *Helianthus annuus* seed extract possesses significant peripheral analgesic activity, likely mediated through inhibition of these inflammatory mediators. The findings from both "tail-flick" and "acetic acid induced writhing" tests provide strong evidence that the *Helianthus annuus* seed extract possesses both central and peripheral analgesic activities. This observation is pharmacologically important, as it suggests that the phytochemical constituents of the extract may exert analgesic effects through multiple mechanisms, including modulation of neural nociceptive pathways as well as inhibition of inflammatory mediators such as prostaglandins.

As presented in Table 3, the ethanolic extract of *Helianthus annuus* seeds also demonstrated significant antipyretic activity in the "brewer's yeast induced pyrexia model". Following administration of yeast to all the animals, there was an increase in rectal temperature (in °F) after 24 hr, indicating that fever had been effectively induced. It was observed that both doses of test drugs and standard drug were effective in reducing the temperature. In addition, after 120 min, decline in temperature in all the treated groups was significant and comparable. Brewer's yeast-induced pyrexia serves as a proven model for assessing antipyretic medications, marked by increased pro-inflammatory cytokines and heightened expression of prostaglandin-synthesizing

enzymes in peripheral tissues and the central nervous system (Duarte *et al.*, 1988). Thus, the present data suggest that the extract may alleviate fever by suppressing pyrogen-induced prostaglandin production and related inflammatory signalling.

A potential explanation for the analgesic and antipyretic effects seen in this study is the phytochemical composition of *Helianthus annuus*. These sunflower seeds contain phenolic acids, flavonoids, terpenes and various other bioactive chemicals recognised for their pharmacological effects. Anti-inflammatory, antioxidant, pain-relieving effects of these compounds are well-known. Efficacy of sunflower extracts has also been found to be significantly affected by phenolic compounds, including chlorogenic acid. The observed decrease of nociception and fever in this study may be explained by the presence of these components in the ethanolic seed extract (Dangarembizi *et al.*, 2018).

Another significant finding of the current research is the dose-response relationship, wherein 200 mg/kg dose of ethanolic extract of *Helianthus annuus* seeds consistently showed higher efficacy than 100 mg/kg dose. In acetic acid writhing and tail-flick models, the higher dose produced effects similar to those of the standard medication. In "brewer's yeast-induced pyrexia model," both doses exhibited a significant reduction in temperature by 120 min, although the higher dose showed a more pronounced effect overall. The reported pharmacological actions are strengthened by this consistent dose-dependent pattern, which also implies that the extract's analgesic and antipyretic effects are unlikely to be incidental. The findings further indicate that the active constituents present in the ethanolic extract are effective within the tested dose range but may demonstrate enhanced activity upon further optimisation or isolation of individual bioactive compounds.

In spite of these promising findings, there are some limitations of the study that should be mentioned. The experiment was restricted to the acute models and therefore does not provide evidence regarding the efficacy of the extract in chronic pain states or prolonged inflammatory conditions. In addition, the specific phytoconstituents responsible for the observed pharmacological effects were neither isolated nor qualified. Assessment of prostaglandin level, cytokine profiling was also not undertaken. Consequently, although the present findings clearly demonstrate significant analgesic and antipyretic effects, further research is necessary to ascertain the pertinent phytoconstituents, elucidate the precise mechanism of action, and assess long-term safety and efficacy of the extract (Takeda & Sashide, 2025).

## CONCLUSION

Ethanolic extract of *Helianthus annuus* seeds has significant analgesic and antipyretic effects in Wistar albino rats, according to the current study. The tail-flick method showed that the extract made reaction time longer, which suggests that it works as a central analgesic. Peripheral analgesic efficacy was demonstrated by the significant reduction in writhing frequency in "acetic acid-induced writhing test." Extract significantly decreased body temperature in "brewer's yeast-induced pyrexia model," demonstrating its potential as an antipyretic. These results indicate that *Helianthus annuus* seed extract may be a valuable natural source of bioactive compounds exhibiting analgesic and antipyretic effects. Nonetheless, additional research is necessary to identify the active components, clarify the precise mechanism of action, and determine long-term safety prior to potential therapeutic use.

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## ABBREVIATIONS

**GBD:** Global Burden of Disease; **COX:** Cyclooxygenase; **PGE2:** Prostaglandin E2; **NSAIDs:** Nonsteroidal Anti-Inflammatory Drugs; **COX-1:** Cyclooxygenase-1; **COX-2:** Cyclooxygenase-2; **KIMS:** Kalinga Institute of Medical Science; **IAEC:** Institutional Animal Ethics Committee; **CCSEA:** Control and Supervision of Experiments on Animals; **SD:** Standard Deviation; **ANOVA:** Analysis of Variance; **DRG:** Dorsal Root Ganglion; **NS:** Normal Saline; **HOD:** Head of Department.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHORS CONTRIBUTIONS

**Dr. Vartika Srivastava:** Concept, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and manuscript review. **Dr. Suman Supreeti:** Concept, design, definition of intellectual content, literature search, clinical studies, experimental studies, manuscript preparation, manuscript editing and manuscript review. **Soham Ghosh, Subham Panda, Saptarshi Hajra:** Concept, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing and manuscript review. **Dr. Chaitali Pattanayak:** Definition of intellectual content, literature search, manuscript preparation, manuscript editing and manuscript review. **Dr. Sougata Sarkar:** Data analysis, statistical analysis, manuscript preparation, manuscript editing and manuscript review. **Dr. Mangala Charana Das:** Concept, design, definition of intellectual content, literature search.

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