

Comparative assessment of analgesic activity between whole plant and parts of *Azadirachta Indica*

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World Journal of Biology Pharmacy and Health Sciences, 2023, 13(01), 401–412

Publication history: Received on 30 October 2022; revised on 06 December 2022; accepted on 09 December 2022

Article DOI: <https://doi.org/10.30574/wjbphs.2023.13.1.0235>

Abstract

Azadirachta Indica is a most common medicinal plant which is use for Antibacterial, Antifungal, Antiulcer, Antiviral, Analgesic, sedative properties.

Objective: The aim of the study was Comparative Assessment of Analgesic Activity between whole plant and parts of *Azadirachta Indica* in experimental animal model.

Methods: The extracts were prepared by maceration method. Analgesic activity was assessed by tail flick method and hot plate method (for central action) and acetic acid-induced writhing test (for peripheral action).

Results: Seed extract, whole plant extract and aspirin showed significant analgesic activity, both central and peripheral, as compared to control ($p < 0.01$). Although Whole plant extract at dose of 500 mg/kg showed better activity than 250 mg/kg ($p < 0.05$).

Keywords: Analgesic; *Azadirachta Indica*; Maceration; Tail flick; Writhing

1. Introduction

Neuropathic pain is pain caused by damage or injury to the neurological system, which includes nerves, the central nervous system, and the spinal cord, and has a diverse aetiology and pathophysiology. Patients with cancer, diabetes, leprosy, AIDS, and cervical disc projection resulting mostly from peripheral neuropathic pain. According to World Health Organization, around 22 % of the world's primary care patients whose suffer There is an urgent need for all healthcare providers and clinicians to address chronic neuropathic pain.

Any member of the category of medications that was used to relieve pain and achieve analgesic. The Greek words anos, which means "without," and algos, which means "pain," are combined to form the word analgesic. These drugs affect the nervous and peripheral nervous systems in a number of ways. These medications are split into numerous groups, including NSAIDs (non-steroidal anti-inflammatory drugs) and others.

Morphine and opium were opioid analgesics and acetic acid chemicals, respectively, as Salicylic Acid derivatives. They differ from anesthetics in that they remove sensation in a reversible manner. [1-4]

The synthesis of 1, 5-benzodiazepines had gotten a lot of attention because of their wide variety of pharmacological, industrial, and synthetic applications. The choice of analgesic treatment is also impacted by the type of pain, which

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means that standard analgesics are less effective for neuropathic pain, and that classes of pharmaceuticals that are not normally considered analgesics, such as antidepressants and anti-epileptics, are often beneficial.

Pain, which is classed as neuralgia, is an unpleasant sensory experience associated with tissue injury. The nerves convey a signal to the brain, allowing the body to experience pain. Pain can be chronic or acute, and it can come and go in cycle.

Whether it was due to tissue damage or not, we've all experienced pain at some point in our lives. We can sometimes ignore pain, but there are occasions when we require medical assistance. [5]

Many plants exist in the globe that are highly useful and effective for pain alleviation. Gastric lesions, which are generated by NSAIDs, as well as tolerance and dependency, include opiates, and the use of these medicines as analgesic agents has not always been successful. As a result, analgesic medications that do not have those side effects are being sought all over the world as alternatives to NSAIDs and opiates. Plant-based medications, which are traditional medicine, have gotten a lot of attention during this process since they are inexpensive, have minimal adverse effects, and are still used by about 80% of the world's population, according to WHO. [6]

1.1. Analgesics are divided into two groups

- Opioid/narcotic/morphine-like analgesics.
- Nonopioid/non-narcotic/aspirin-like/antipyretic or anti-inflammatory analgesics

1.1.1. Opioid analgesics

Opium which is dark brown, resinous material get from poppy (*Papaver somniferum*) capsule. It contains 2 types of alkaloids.

- Phenanthrene derivatives :
 - Morphine (10% in opium)
 - Codeine (0.5% in opium)
 - Thebaine (0.2% in opium), (Nonanalgesic).
- Benzoisoquinoline derivatives:
 - Papaverine (1%) Nonanalgesic Noscapine (6%).

Nonselective COX inhibitors

- Salicylates:Ex- Aspirin.
- Propionic acid derivatives: Ex- Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen.
- Fenamate: Ex- Mephenamic acid.
- Enolic acid derivatives:Ex- Piroxicam, Tenoxicam.
- Acetic acid derivatives: Ex- Ketorolac, Indomethacin, Nabumetone.
- Pyrazolone derivatives: Ex- Phenylbutazone, Oxyphenbutazone.

Preferential COX-2 inhibitor:

Ex- Diclofenac, Aceclofenac

Selective COX-2 inhibitors

Ex- Celecoxib, Etoricoxib, Parecoxib

1.1.2. Analgesic-antipyretics with poor anti-inflammatory action

- Paraaminophenol derivative: ex -Paracetamol (Acetaminophen).
 - Pyrazolone derivatives: ex-Metamizol (Dipyrone), Propiphenazone.
 - Benzoxazocine derivative: ex-Nefopam
- Results and discussion

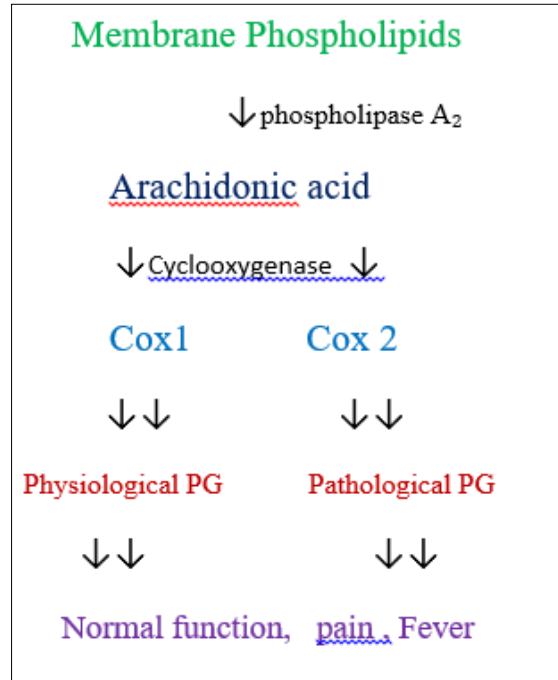


Figure 1 Pain Pathway

2. Morphine

Morphine is the principal alkaloid in opium and is widely used till today. It is referred regarded as a prototype for these reasons.

2.1. Pharmacological actions

- CNS: Morphine interacts with opioid receptors in the CNS to act as a depressant and stimulant (as well as antagonistically) with opioid receptors (for which it has the highest affinity).

The depressant actions are:

- Analgesia: Morphine is a highly effective analgesic. Visceral pain that is poorly localised and dull is eased better than highly marked somatic pain.
- Sedation: Morphine is detected, but it is not the same as that produced by hypnotics. Drowsiness and apathy toward one's surroundings as well as one's own body might arise without the presence of motor incoordination.
- CVS: Morphine causes vasodilatation due to: (a) depression of vasomotor centre. (b) Histamine released (c) direct action decreasing tone of blood vessels.
- GIT: The enteric plexus neurons and the gastrointestinal mucosa have opioid receptors. Morphine has a strong effect on gastrointestinal motility as well as fluid dynamics across the mucosa of the gastrointestinal tract. Constipation is a common side effect of morphine.

2.2. Adverse effects

2.2.1. Acute morphine poisoning

It could be suicide, unintentional, or a side effect of a medicine. 50 mg of morphine i.m. generates significant toxicity in the non-tolerant adult. The fatal dose for humans is estimated to be around 250 mg. Stupor or coma, flaccidity, shallow and irregular breathing are all indicators of a pharmaceutical action that has been intensified. Convulsions, cyanosis, pinpoint pupil, drop in blood pressure, and shock; cyanosis, pinpoint pupil, drop in blood pressure, and Pulmonary oedema occurs near the end of life, and respiratory failure is the cause of death.

- Treatment

It consists of respiratory support (positive pressure respiration also prevents the formation of pulmonary edema *Azadirachta Indica*) and blood pressure management (i.v. fluids, vasoconstrictors). To eliminate unabsorbed drugs, gastric lavage should be performed with pot. permanganate. When morphine has been injected, lavage is recommended.

Because it is a basic medication, it is partitioned to the acidic stomach juice, where it ionises and does not diffuse back into the blood.

Specific antidote: Naloxone 0.4–0.8 mg i.v., repeated every 2–3 minutes until respiration returns, is the preferred particular antagonist because it acts quickly. It has no agonistic properties and does not, in and of itself, suppress respiration. Because of the brief duration of action and the need to repeat naloxone every 1–4 hours depending on the reaction.

3. Classification of opioids

- Natural opium alkaloids: Morphine, Codeine.
- Semisynthetic opiates: Diacetylmorphine (Heroin), Pholcodeine, Ethylmorphine.
- Synthetic opioids: Pethidine (Meperidine), Fentanyl, Methadone, Dextropropoxyphene, Tramadol.

3.1. Codeine

It is methyl-morphine. It's contained in opium naturally and is largely converted to morphine in the body. It has a lower potency (1/10th that of morphine) and is less effective. It's also a partial agonist with a limited maximal action at the opioid receptor. It can only be used to treat mild to moderate pain and has a similar analgesic effect as aspirin (60 mg codeine vs. 600 mg aspirin).

3.2. Pethidine (Meperidine)

Pethidine is a synthetic atropine with atropine-like effects. Despite the fact that it has no structural resemblance to morphine, naloxone binds to opioid receptors and prevents its effects. There are some noteworthy differences when compared to morphine:

- In analgesic potency, dose to dose 1/10th; yet, analgesic efficacy approaches morphine and is greater than codeine.
- The beginning of action is faster after an i.m. injection, but the duration is shorter (2–3 hours).
- It has no effect on cough suppression.
- Miosis, constipation, and urine retention are reduced as the spasmodic effect on smooth muscles is reduced.

Herbal treatments that are effective analgesics, as well as anti-inflammatory and antispasmodic. Herbs and pharmaceutical medications, on the other hand, have a lot of functions in common. They are neither interchangeable nor analogous in any way. Herbal formulations' medicinal efficacy is contingent on good diagnosis and cautious prescription.

When analgesic herbs are utilised correctly, they can be a powerful alternative to the drug of choice for pain relief. [7]

The popularity of herbal medicine has soared in recent years all across the world. These items are not regulated by the Food and Drug Administration and are not subject to the same level of scrutiny as traditional pharmaceuticals. Herbal supplements are regularly used in conjunction with well-known pharmaceuticals by patients. [8]

Being a natural pain reliever, any form of analgesic herb has the advantage of having no side effects, unlike other chemically created pain relievers. Because of their analgesic properties, several analgesic herbs are usually referred to as joint herbs which provide relief from joint symptoms such as arthritis, neck and back pain, and tendonitis. These medicinal herbs, in truth, are anti-inflammatory herbs that are used to treat pain caused by joint inflammation. [9]

Azadirachta Indica (Family: Meliaceae) contains antifungal, antidiabetic, antibacterial, antiviral, contraceptive, and sedative qualities according to Ayurveda. It's been tested for cancer, inflammation, ulcers, immunological disorders,

hyperlipidemia, and liver disease, among other things. It's also thought to have anti-nociceptive properties. Herbs with a strong potential for developing new medications of enormous utility to people as a natural fund. Many people are on the verge of discovering new biologically active properties in plants. [10]

Infertility, convulsions, diarrhoea, dysentery, gonorrhoea, flatulence, tonsillitis, and bacterial infections are some of the disorders that have been successfully treated using herbal medication. malaria, epilepsy and fungal infections, mental illness and worm infections. [11]

Natural selection has created biologically potent and active natural chemicals that can serve as lead through moderation and competition amongst organisms, and have been polished by current techniques to give more defining active drugs. [12]

Alkaloids, saponin, flavonoids, tannins, and phenolic compounds are the most important bioactive molecules, which are mostly secondary metabolites. These phytochemicals have the potential to harm microbial cells. [13] Plant polyphenols have sparked a lot of interest, as evidenced by the numerous articles devoted to various aspects of these substances. [14,15]

Polyphenols are plant metabolites generated from L-phenylalanine that include numerous phenol groups (i.e. aromatic rings with hydroxyls). [16]

The phenolic acids, which contain polymeric structures such as hydrolyzable tannins, lignans, stilbenes, and flavonoids, are the most important category of polyphenols. Flavonoids, which include flavonols, flavones, isoflavones, flavanones, and anthocyanidins, are renowned for their antioxidant and antibacterial biological effects, with flavanols being the most well-known. [17]

Saponins are a varied category of phytochemicals with a fat-soluble nucleus (aglycone) that is either a triterpenoid (C-30) or a neutral or alkaloid steroid (C-27) connected to one or more water-soluble sugars (glycone) side chains via ester bonds at distinct carbon positions. [18]

Soybean, alfalfa, and quillaja [18] have mostly triterpenoid saponins, whereas yucca, tomato, and oats have mostly steroid saponins. [18] Saponins have a wide range of biological effects, including hemolytic and anti-inflammatory effects.

Medicinal trees that are utilized in the development of new drugs impart on the infusion of unique compounds or materials for disease healing. The evaluation of flora from the traditional African system of medicinal plants supplies us with a wealth of information about disease therapy. The antimicrobial activity of the neem tree, which is used in Ethiopia for traditional treatment of a range of maladies, has yet to be discovered, thus the current study's goal is to evaluate the phytochemical screening and antibacterial resources of *Azadirachta Indica* herbal bark and seeds.

4. Materials and Methods

4.1. Plant material

- The whole Plant *Azadirachta Indica* was collected in Nov 2021 from West Burdwan district West Bengal, the plant specimen was authenticated from GCTS Asansol (voucher specimen no.YMA2) by Dr. ManikBaral.
- The collected plant parts were dried for one week.
- Ground into a coarse powder with the help of a suitable grinder.
- The powder was kept in an airtight container and kept in a cool, dark and dry place.
- Leaves, Bark, Root are mixed proportionally.
- Seeds was separated from the plants

4.2. Preparation of the extract of mixture component

- 150 gm of mixture material was taken in a clean flat glass container
- soaked in 900 ml of methanol
- The container with its contents was sealed and kept for a period of 7 days
- occasional shaking
- Filtration by cotton material Then it was filtered through Whatman filter paper

- The filtrate was evaporate during rotary evaporator

4.3. Extraction of seed

- 50 gm of seed powder was taken in glass container.
- Container was stocked 150 ml of methanol.
- Container with its contents was sealed and kept for a period of 7 days.
- Occasional shaking.
- Filtration by cotton material Then it was filtered through Whatman filter paper.
- The filtrate was evaporating during rotary evaporation.

4.4. Preliminary Phytochemical Studies

4.4.1. Qualitative Analysis

- Phytochemical screening of the prepared mixture extracts and seed was conducted with various qualitative tests to identify the presence of chemical constituents. [19]
- Mixture contain Flavonoids, Glycosides, Alkaloids and Saponin. [20]
- Seed was contains Alkaloids, Carotenoids, Saponins, Anthraquinone Cardiac glycosides, Flavonoids. [21]

4.5. Animals required

- Species and Strain: Swiss albino mice
- Weight: Albino mice (20-25 gm)
- Gender :Male

The animals were kept in stainless steel cages. The housed at an ambient temperature of between 25- 27°C and relative humidity of about 50-55% with free access to feed and water., The study protocol was accepted by the Gupta College of Technological Sciences' ethical committee [Protocol no - GCTS/IEC/2021/Aug/08]

4.6. Tail flick method

The central analgesic activity was tested by tail flick method in Albino rats. Healthy rats of either sex weighing 30 g were fasted overnight and divided into eight groups with six animals in each group. The tail flick latencies (reaction time) of the animals were measured by analgesiometer. Reaction time to radiant heat was taken and set down the tip (last 2 cm) of the tail on the radiant heat source. The final point will be tail withdrawal from the heat (flicking response).A cut of period of 10 sec will be observed to prevent damage to the tail.

The tail flick latencies will be recorded at pre-drug, 15, 30, 60, 90 min after administration of drugs. Tramadol will be taken as standard drug. [22]

4.7. Hotplate Method

Albino mice of both sexes were randomly divided into five groups, each with five individuals. 12 hours of fasting with plenty of fresh water. Each mouse was placed on a hot plate that was kept at 55°C for 10 minutes, and the pain reaction time was measured, (PRT) or latency period determined with a stop watch was recorded which represents the time taken for the mice react to the pain produce. The response to pain produce, study included; raising, jumping and licking of hind foot. Orally, a methanolic extract of the combination and seed was given. The pain threshold (Number licking of paw/jumping) was measured at 30, 60, 90 min after administration of standard and test solution. [23]

4.8. Acetic acid induced writhing method

The peripheral analgesic activity of Albino mice was examined using a Writhing test induced by glacial acetic acid. Healthy mice of either sex weighing 30 gm were fasted overnight and divided into five groups. Each groups contain six animals .Acetic Acid induce for producing pain after one hour administration of drugs. 10 ml/kg is the recommended dose. For 20 minutes, the number of writhing responses was counted and recorded. Aspirin was taken as standard drug at a dose of 100 mg/kg. [24]

4.9. Statistical analysis

Statistical analysis was done using one way ANOVA followed by Tukey HSD Test. Significance level of $p < 0.05$ was considered as significant. [25]

5. Results

5.1. Central Analgesic Activity

From this study, we can see that the ethanolic extracts of Seed and whole plant of *Azadirachta Indica* and standard drug Tramadol showed significant central analgesic activities when compared to control. Seed extract (500 mg/kg) has considerably lower central analgesic effectiveness than whole plant extract (500 mg/kg). Tramadol's analgesic activity was substantially higher than that of traditional analgesics.

Table 1 The activity of central analgesic of methanolic extract of *Azadirachta Indica* whole plant and seed extracts on the tail flick response

Drugs	15 min	30min	60min	90 min
Control	3.31± 0.39	3.32±0.35	3.4± 0.18	3.86± 0.27
Naloxone	3.12±0.07	2.92± 0.16	2.61±0.37	2.43± 0.37
Seed Extract (250mg)	3.20± 0.10	3.28± 0.12	3.57±0.14	3.65±0.09
Seed Extract (500mg)	3.72± 0.19	4.07± 0.50	4.19±0.33	4.45±0.38
SeedExtract(500mg) + Naloxone	3.52± 0.021	3.39±0.035	3.69± 0.023	4.23±0.39
Whole plant Extract (500mg)	4.29± 0.063	4.64± 0.13	4.84±0.136	5.24±0.24
Whole plant Extract (500mg) + Naloxone	4.16± 0.068	4.46±0.078	4.57±0.158	4.98±0.082
Tramadol	4.82± 0.07	5.10± 0.11	5.57±0.28	6.05±0.32

n = 6; $p < 0.01$, $p < 0.01$, $p < 0.02$, $p < 0.01$ when compared to standard; ANOVA followed by Tukey HSD test.

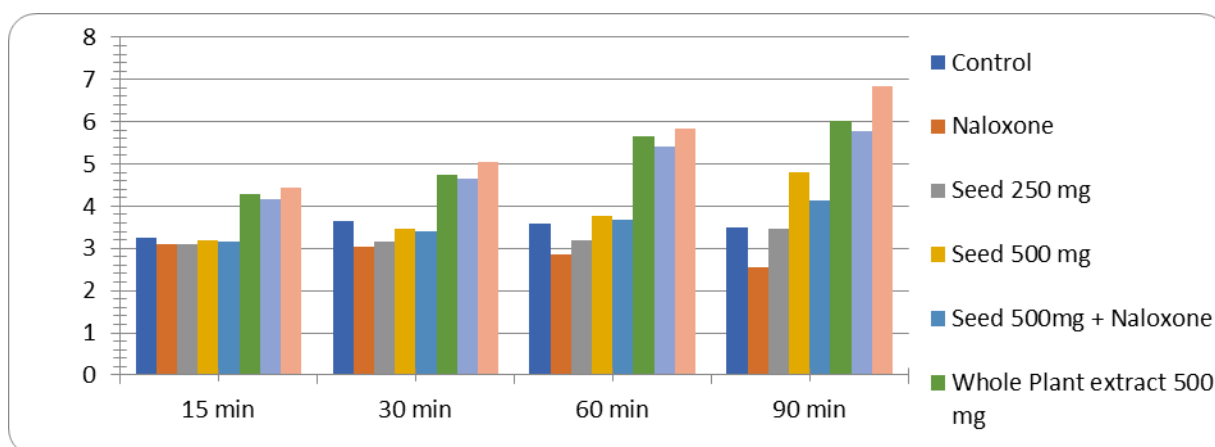


Figure 2 This histogram showing the various response in mice on tail flick having cont. temp $55 \pm 2^\circ\text{C}$ in 15 min, 30 min, 60 min, 90 min after drug administration. Histogram is plotted between control, standard, mixture extract, seed extract. X axis in Time (min) and Y axis in Withdrawal time of tail between control, standard, mixture extract, seed extract

5.2. Hot Plate Method

Table 2 Effect of *A.Indica* Extract on Hot Plate Induced Pain in Mice

Group	30min	60min	90 min
Standard	11.66±1.03	12.33±2.25	17.88±1.16
Seed (250mg/kg)	4.5±0.54	6.33±1.03	7.5±1.04
Seed extract (500mg/kg)	5±0.63	8.5±1,04	9.5±0.54
Whole plant extract (500mg/kg)	7.83±0.75	9.6±2.25	14.5±2.42
Control	4±0.43	5±0.53	6±0.67c

n=6and p<0.01 , p<0.04 , p<0.01 when compared to standard; ANOVA followed by Tukey HSD test.

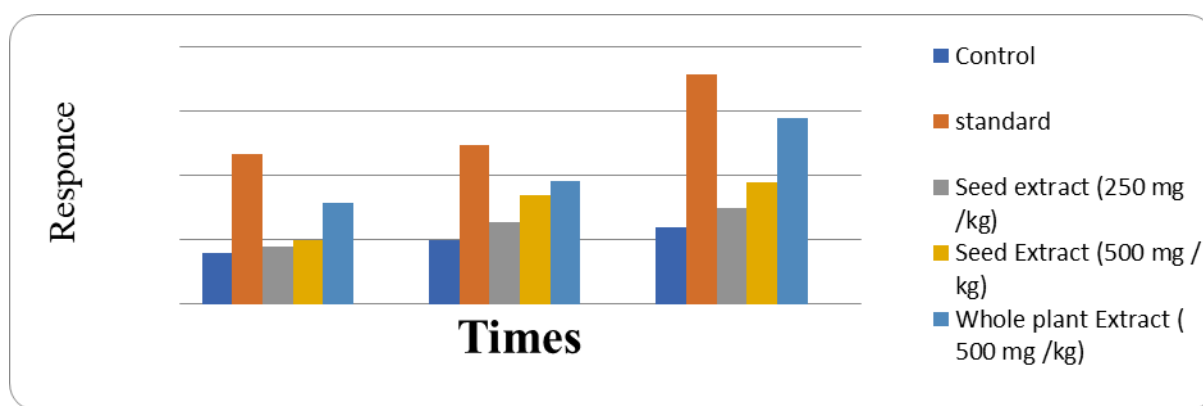


Figure 3 This histogram showing the various response in mice on hot plate having cont. temp 55±2 °C in 30 min, 60 min, 90 min after drug administration. Histogram is plotted between control, standard, mixture extract, seed extract. X axis in Time (min) and Y axis in Reaction time

5.3. Peripheral Analgesic Activity

On an acetic acid-induced writhing test, the methanolic extract of *Azadirachta Indica* whole plant and seed extracts had peripheral analgesic efficacy.

Table 3 Peripheral Analgesic Effect

Group	Drug	Number of writhing movements (20 min)
Control	10ml/kg	42.83±1.47
Seed extract	250mg/kg	32.33±1.12
Seed extract	500mg/kg	23.5±1.87
Whole Plant extract	500mg/kg	18.16±1.47
Aspirin	100 mg / kg	14.5±1.64

n=6andp<0.01 when it compared to standard; ANOVA followed by Tukey HSD test

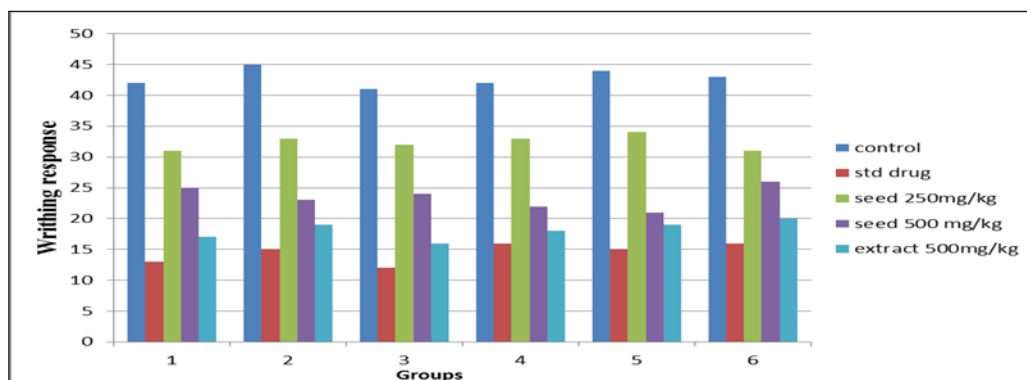


Figure 4 This histogram showing inhibition of writhing response after induced acetic acid in mice Histogram is plotted between control, standard, mixture extract, seed extract

6. Discussion

Using an acetic acid-induced writhing response to determine the analgesic efficacy of *Azadirachta Indica* for peripheral analgesic activity. In central analgesic activity we can check the tail immersion and hot plate models. Whatever analgesic medication tests was used to assess nociception, which was the animal's sensitivity to painful stimuli. [26] From this above study which can show that methanolic extracts of mixture component and seed of *A. indica* produced significant analgesia, in both centrally and peripherally. The central action was mediated via opioid receptors which was seen with the tail flick responses. Pre-treatment with naloxone which was significantly reduce the reaction time creating hyperalgesia. Naloxone which was given along with the test drug, there was remarkable enhance in reaction time as compared to naloxone alone without causing hyperalgesia. Partial agonistic activity for the opioid receptors as likely mechanism of central analgesic action. At 500 mg/kg, whole plant extract considerably reduced the mean number of abdominal constrictions. In the hot plate model, seed extracts of 500 mg/kg and 250 mg/kg were less effective than whole plant extracts at concentrations of 500 mg/kg. The extract of whole plant extract 500 mg/kg significantly increased the pain reaction time and the whole plant extract at the dose of 500 mg/kg was show a better analgesic effect than seed extract. The tail flick and hot plate models which had been used to study centrally acting analgesics. According to the findings, the whole plant extract had analgesic effects in the tail immersion and hot plate models. [27] The acetic acid-induced writhing reflex was a visceral pain model that can be used to screen analgesic medicines. The level of analgesia in acetic acid-induced models is also measured by the percent reduction in the number of abdominal constriction. [28] In this experiment, the reference drug and *A. indica* at 500 mg/kg, whole plant extract considerably reduced the mean number of abdominal constrictions. or writhes which was dose dependent comparing seed extract 500 mg/kg and 200 mg/kg. Acetic acid-induced writhing model which was produces pain sensation by trigger the response of inflammation which is pain stimulus leads to secret arachidonic acid from tissue. [29] The analgesic effect of *Azadirachta Indica* seen in this experiment may be mediated through peripheral pain mechanism and or through suppression of prostaglandin pathway since it had been observed that any vehicle that decreases the number of writhing will signified analgesia. Inhibition of prostaglandin production reduced a peripheral mechanism of pain. [30] Aspirin which was used for relaxation from inflammatory pain by inhibiting the formation of pain substances in the peripheral tissues. Prostaglandins and bradykinin which were indicate to producing pain. [31] Prostaglandin in pain by direct stimulation of sensory nerve endings and also sensitize sensory nerve endings to other pain arousing stimuli. [32] Additionally, prostaglandins, notably PGE1, which was known to act on the cell membrane during inflammatory conditions, modify the shape of cell membrane lipoproteins significantly. Due to this reason imbalance of cell membrane furthering to degenerative cellular changes. Therefore, that was likely that *A. indica* whole plant and seed extracts might decrease the formation of these antagonize the action of these substances. Hence it was apply on acetic acid-induced writhing test which showed peripheral analgesic activity. [33] On comparing the analgesic property of methanolic extract of whole plant of *A. indica*, that was showed by a dose dependent central and peripheral analgesic and central activity. Seed extract 500 mg/kg was showing comparatively less active than mixture extract 500 mg/kg. Also the analgesic action of whole plant extract 500 mg/kg was more portent comparing the seed extract 500 mg/kg. Aspirin was most potent all of these. The analgesic activity, both central and peripheral, of all drugs in decreasing order was found to be as: Aspirin then whole plant extract 500 mg/kg then seed extract 500 mg/kg then seed extract 250 mg/kg. [34].

7. Conclusion

One of the most important sources of medications is plants. The importance of medicinal plants in enhancing human health's ability. From ancient times, unpleasant and difficult situations which had been frequently reported all across the world. In medicinal plants, which is secondary metabolites, which are potential drug sources and therapeutically relevant, are plentiful. Plant extracts are becoming increasingly used as medicinal agents. Neem is a plant with pharmacological properties that can be used as a panacea. Neem may work via inhibiting the prostaglandin pathway or by acting on the peripheral pain system. However, more research was needed to isolate and characterise the bioactive compound(s) as well as determined the specific mechanism of action. According to the literature review, Neem was a potential source of antibacterial, antifungal, antiulcer, antiviral, and analgesic medications, as well as antipyretic action in neem oil and many other products. Using many parameters such as the hot plate method, tail flick method, and acetic acid induce model, methanolic whole extract of *A.indica* which at dosages of 500 mg/kg body weight, exhibited a significant analgesic effect. These findings demonstrated that the extract of *A. indica* was a mixture of many chemicals, and fractionation of the extract could result in an active analgesic. Since the plant extract considerably reduced the number of writhes generated by acetic acid. The acute toxicity research found no deaths, indicating that the herb is safe to use. Purified extracts that can be used in future studies to better characterise pharmacological and toxicological properties, such as study into the mechanisms behind the central and peripheral analgesic effects. However, more research was needed to understand the mechanism behind this effect. Finally, it's worth noting that neem extracts had other features that affect industrial markets, their potential such as fungicides, bactericides, and surface coatings (medical, residential, and commercial). As a result, neem and its extracts have a wide range of applications that go beyond conventional medical folklore. We may now utilize these extracts as current medical adjuvants, knowing their potential, thanks to scientific and technological advancements. We now know how to expand on the evolution of knowledge and even provide them more practical uses.

Compliance with ethical standards

Acknowledgments

The authors are thankful to the Management and Principal, Gupta College Of Technological Sciences, Asansol for providing the facilities to carry out this study.

Disclosure of conflict of interest

There is no conflict of Interest.

Statement of ethical approval

For performing experiment on animals, ethical clearance for the study was accorded by I.A.E.C. of Gupta College Of Technological Sciences, Asansol, (bearing registration number 955/PO/Re/S/06/CPCSEA) in resolution number GCTS/IEC/2021/Aug/08. The In vitro methods were executed by using Albino mice (male). Animals were obtained from the animal house of Gupta College Of Technological Sciences, Asansol.

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