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# "EVALUTION OF ANALGESIC ACTIVITY OF METHANOLIC EXTRACT OF SIDA ACUTA ON RATS USING BY EDDY'S HOT PLATE METHOD"

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**Abstrsct:** Evalution of analgesic activity of methanolic extract of sida acuta on rats using by eddy's hot plate. Pain was induced in Wistar albino rats by all Formulations for analgesic activity were administered orally aqueous diclofenac sodium. The dose was set to 10mg/kg body weight. For the assessment of analgesic activity the animals divided into four groups each composed of five animals. All groups received intraperitoneal injection (maximum 1 ml as per ethical norms). Leafs of ***sida acuata*** plant were collected, dried the flowers.Dried materials were taken, crushed it to coarse powder.The materials were weighed and transfer in to a clean round bottom flask.Sufficient quantity of methanol was added till it totally immersed and maceration it for seven days.The extract was filtered by using muslin cloth.The obtain filtrate was evaporated and cooled to dryness at $45^0$ to $55^0$c. Until it become like a semisolid.Animals were divided into four groups.Normal control group was treated with saline,test group was treated with extract low dose 100 mg/kg and extract at high dose 200 mg /kg and as standard treated with diclofenac sodium (9 mg/kg). The reaction time was recorded before (0 min) and at 15, 30, 45, and 60 min after the administration of the treatments. The maximum reaction time was fixed at 45 sec to prevent any injury to the tissues of the paws. If the reading exceeds 45 sec, it would be considered as maximum analgesia. The present study showed that the pain relief in test group where it was compared with the positive standard group.It showed the analgesic activity.

Keywords: Sida acuta, Diclofenac sodium, Maceration, Methanol, Eddy's hot plate, Analgesic activity.

## INTRODUCTION

An **analgesic** or **painkiller** is any member of the group of drugs used to achieve analgesia, relief from pain.

Analgesic drugs act in various ways on the peripheral and central nervous systems. They are distinct from anesthetics, which reversibly eliminate sensation. Analgesics include Paracetamol (known in North America as acetaminophen or simply APAP), the non-steroidal anti-inflammatory drugs (NSAIDs) such as the salicylates, and opioid drugs such as morphine and oxycodone.

In choosing analgesics, the severity and response to other medication determines the choice of agent; the World Health Organization (WHO) pain ladder specifies mild analgesics as its first step.

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Analgesic choice is also determined by the type of pain: For neuropathic pain, traditional analgesics are less effective, and there is often benefit from classes of drugs that are not normally considered analgesics, such as tricyclic antidepressants and anticonvulsants.

**Major classes**

**PARACETAMOL AND NSAIDs**

The exact mechanism of action of Paracetamol is uncertain but appears to act centrally in the brain rather than peripherally in nerve endings. Aspirin and the other non-steroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenases, leading to a decrease in prostaglandin production. In contrast to Paracetamol and the opioids, this reduces not only pain but inflammation as well.

Paracetamol has few side-effects and is regarded as generally safe in low and infrequent doses as prescribed or per manufacturer's instructions, otherwise use can lead to potentially life-threatening liver damage and occasionally kidney damage. Side effects include bloody or black, tarry stools, bloody or cloudy urine, fever with or without chills (not present before treatment and not caused by the condition being treated), pain in the lower back and/or side (severe and/or sharp), pinpoint red spots on the skin, skin rash, hives, or itching, sore throat (not present before treatment and not caused by the condition being treated), sores, ulcers, or white spots on the lips or in the mouth, sudden decrease in the amount of urine, unusual bleeding or bruising, unusual tiredness or weakness, yellow eyes or skin.

While Paracetamol is usually taken orally or rectally, an intravenous preparation introduced in 2002 has been shown to improve pain relief and reduce opioid consumption in the perioperative setting.

NSAIDs can predispose to in some patients peptic ulcers, renal failure, allergic reactions, and occasionally tinnitus with excess dosage, and they can increase the risk of hemorrhage by affecting platelet function. The use of aspirin in children under 16 suffering from viral illness has been linked to Reye's syndrome, a rare but severe liver disorder.

Nonsteroidal anti-inflammatory drugs also called nonsteroidal anti-inflammatory agents/analgesics (NSAIAs) or nonsteroidal anti-inflammatory medicines (NSAIMs), are a drug class that groups together drugs that provides analgesic (pain-killing) and antipyretic (fever-reducing) effects, and, in higher doses, anti-inflammatory effects.

The term *nonsteroidal* distinguishes these drugs from steroids, which, among a broad range of other effects, have a similar eicosanoid-depressing, anti-inflammatory action. First used in 1960, the term served to distance new drugs from steroid related iatrogenic tragedies.

As analgesics, NSAIDs are unusual in that they are non-narcotic and thus are used as a non-addictive alternative to narcotics.

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The most prominent members of this group of drugs, aspirin, ibuprofen and naproxen, are all available over the counter in most countries. Paracetamol (acetaminophen) is generally not considered an NSAID because it has only little anti-inflammatory activity. It treats pain mainly by blocking COX-2 mostly in the central nervous system, but not much in the rest of the body.

Most NSAIDs inhibit the activity of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), and thereby, the synthesis of prostaglandins and thromboxane's. It is thought that inhibiting COX-2 leads to the anti-inflammatory, analgesic and antipyretic effects and that those NSAIDs also inhibiting COX-1, particularly aspirin, may cause gastrointestinal bleeding and ulcers.

**Medical uses**

NSAIDs are usually used for the treatment of acute or chronic conditions where pain and inflammation are present.

NSAIDs are generally used for the symptomatic relief of the following conditions:

- Osteoarthritis
- Rheumatoid arthritis
- Mild-to-moderate pain due to inflammation and tissue injury
- Low back pain
- Inflammatory arthropathies (e.g., ankylosing spondylitis,psoriaticHYPERLINK "https://en.wikipedia.org/wiki/Psoriatic_arthritis" arthritis, reactive arthritis)
- Headache
- migraine
- Acute gout
- Dysmenorrhea (menstrual pain)
- Muscle stiffness and pain due to Parkinson's disease
- They are also given to neonate infants whose ductus arteriosus is not closed within 24 hours of birth

Aspirin, the only NSAID able to irreversibly inhibit COX-1, is also indicated for inhibition of platelet aggregation. This is useful in the management of arterial thrombosis and prevention of adverse cardiovascular events. Aspirin inhibits platelet aggregation by inhibiting the action of thromboxane $A_{2}$HYPERLINK "https://en.wikipedia.org/wiki/Thromboxane_A2"2.

**CONTRAINDICATIONS:-**

NSAIDs may be used with caution by people with the following conditions:

- Irritable bowel syndrome

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- Persons who are over age 50, and who have a family history of GI(gastrointestinal) problems
- Persons who have had past GI problems from NSAID use

NSAIDs should usually be avoided by people with the following conditions

- Peptic ulcer or stomach bleeding ,Uncontrolled hypertension, Kidney disease
- People that suffer with Inflammatory Bowel Disease (Crohn's Disease or Ulcerative Colitis)
- Past transient ischemic attack (excluding aspirin) ,Past stroke (excluding aspirin)
- Past myocardial infarction (excluding aspirin), Coronary artery disease (excluding aspirin)
- Undergoing coronary artery bypass surgery, Taking aspirin for heart
- In third trimester of pregnancy,Persons who have undergone gastric bypass surgery
- Persons who have a history of allergic or allergic-type NSAID hypersensitivity reactions, e.g. aspirin-induced asthma

**ADVERSE EFFECTS:-**

The widespread use of NSAIDs has meant that the adverse effects of these drugs have become increasingly common. Use of NSAIDs increases risk of having a range of gastrointestinal (GI) problems. When NSAIDs are used for pain management after surgery they cause increased risk of kidney problems.

An estimated 10–20% of NSAID patients experience dyspepsia. In the 1990s high doses of prescription NSAIDs were associated with serious upper gastrointestinal adverse events, including bleeding. Over the past decade, deaths associated with gastric bleeding have declined.

NSAIDs, like all drugs, may interact with other medications. For example, concurrent use of NSAIDs and quinolones may increase the risk of quinolones' adverse central nervous system effects, including seizure.

**COMBINATIONAL RISK:-**

If a COX-2 inhibitor is taken, a traditional NSAID (prescription or over-the-counter) should not be taken at the same time[] In addition, people on daily aspirin therapy (e.g., for reducing cardiovascular risk) must be careful if they also use other NSAIDs, as these may inhibit the cardioprotective effects of aspirin.

Rofecoxib (Vioxx) was shown to produce significantly fewer gastrointestinal adverse drug reactions (ADRs) compared with naproxen. This study, the VIGOR trial, raised the issue of the cardiovascular safety of the coxibs. A statistically significant increase in the incidence of myocardial infarctions was observed in patients on rofecoxib. Further data, from the APPROVe trial, showed a statistically significant relative risk of cardiovascular events of 1.97 versus placebo which caused a worldwide withdrawal of rofecoxib in October 2004.

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Use of methotrexate together with NSAIDS in rheumatoid arthritis is safe, if adequate monitoring is done.

**CARDIOVASCULAR:-**

NSAIDs aside from aspirin, both newer selective COX-2 inhibitors and traditional anti-inflammatories, increase the risk of myocardial infarction and stroke. They are not recommended in those who have had a previous heart attack as they increase the risk of death and/or recurrent MI. Evidence indicates that naproxen may be the least harmful out of these. NSAIDs aside from (low-dose) aspirin are associated with a doubled risk of heart failure in people without a history of cardiac disease. In people with such a history, use of NSAIDs (aside from low-dose aspirin) was associated with a more than 10-fold increase in heart failure. If this link is proven causal, researchers estimate that NSAIDs would be responsible for up to 20 percent of hospital admissions for congestive heart failure. In people with heart failure, NSAIDs increase mortality risk (hazard ratio) by approximately 1.2–1.3 for naproxen and ibuprofen, 1.7 for rofecoxib and celecoxib, and 2.1 for diclofenac.

**Allergy/allergy-like hypersensitivity reactions**

A variety of allergic or allergic-like NSAID hypersensitivity reactions follow the ingestion of NSAIDs. These hypersensitivity reactions differ from the other adverse reactions listed here which are toxicity reactions, i.e. unwanted reactions that result from the pharmacological action of a drug, are dose-related, and can occur in any treated individual; hypersensitivity reactions are idiosyncratic reactions to a drug. Some NSAID hypersensitivity reactions are truly allergic in origin: **1)** repetitive IgE-mediated urticarial skin eruptions, angioedema, and anaphylaxis following immediately to hours after ingesting one structural type of NSAID but not after ingesting structurally unrelated NSAIDs; and **2)**Comparatively mild to moderately severe T cell-mediated delayed onset (usually more than 24 hour), skin reactions such as maculopapular rash, fixed drug HYPERLINK "https://en.wikipedia.org/wiki/Fixed_drug_eruption"eruptions,photosensitivityHYPERLINK "https://en.wikipedia.org/wiki/Photosensitivity_reaction" reactions, delayed urticaria, and contact dermatitis; or **3)** far more severe and potentially life-threatening t-cell mediated delayed systemic reactions such as theDRESSHYPERLINK "https://en.wikipedia.org/wiki/DRESS_syndrome" syndrome, acute generalized HYPERLINK "https://en.wikipedia.org/wiki/Acute_generalized_exanthematous_pustulosis"exanthematousHY PERLINK "https://en.wikipedia.org/wiki/Acute_generalized_exanthematous_pustulosis" HYPERLINK "https://en.wikipedia.org/wiki/Acute_generalized_exanthematous_pustulosis"pustulosis, the Stevens–Johnson syndrome, and toxic epidermal HYPERLINK "https://en.wikipedia.org/wiki/Toxic_epidermal_necrolysis"necrolysis. Other NSAID hypersensitivity reactions are allergy-like symptoms but do not involve true allergic mechanisms; rather, they appear due to the ability of NSAIDs to alter the metabolism of arachidonic acid in favor of forming metabolites that promote allergic symptoms. Afflicted

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individuals may be abnormally sensitive to these provocative metabolites and/or overproduce them and typically are susceptible to a wide range of structurally dissimilar NSAIDs, particularly those that inhibit COX1. Symptoms, which develop immediately to hours after ingesting any of various NSAIDs that inhibit COX-1, are: **1)** exacerbations of asthmatic and rhinitis (see aspirin-induced asthma) symptoms in individuals with a history of asthma or rhinitis and **2)**exacerbation or first-time development of wheals and/or angioedema in individuals with or without a history of chronic urticarial lesions or angioedema.

**Mechanism of action**

Most NSAIDs act as nonselective inhibitors of the enzyme cyclooxygenase (COX), inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. This inhibition is competitively reversible (albeit at varying degrees of reversibility), as opposed to the mechanism of aspirin, which is irreversible inhibition. COX catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (itself derived from the cellular phospholipid bilayer by phospholipase A$_{\text{HYPERLINK "https://en.wikipedia.org/wiki/Phospholipase_A2"2}}$). Prostaglandins act (among other things) as messenger molecules in the process of inflammation. This mechanism of action was elucidated by John Vane (1927–2004), who received a Nobel Prize for his work (see Mechanism of action of aspirin).

COX-1 is a constitutively expressed enzyme with a "house-keeping" role in regulating many normal physiological processes. One of these is in the stomach lining, where prostaglandins serve a protective role, preventing the stomach mucosa from being eroded by its own acid. COX-2 is an enzyme facultatively expressed in inflammation, and it is inhibition of COX-2 that produces the desirable effects of NSAIDs.

When nonselective COX-1/COX-2 inhibitors (such as aspirin, ibuprofen, and naproxen) lower stomach prostaglandin levels, ulcers of the stomach or duodenum internal bleeding can result.

NSAIDs have been studied in various assays to understand how they affect each of these enzymes. While the assays reveal differences, unfortunately different assays provide differing ratios.

The discovery of COX-2 led to research to development of selective COX-2 inhibiting drugs that do not cause gastric problems characteristic of older NSAIDs.

Paracetamol (acetaminophen) is not considered an NSAID because it has little anti-inflammatory activity. It treats pain mainly by blocking COX-2 mostly in the central nervous system, but not much in the rest of the body.

However, many aspects of the mechanism of action of NSAIDs remain unexplained, and for this reason further COX pathways are hypothesized. The COX-3 pathway was believed to fill some of this gap but recent findings make it appear unlikely that it plays any significant role in humans and alternative explanation models are proposed.

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NSAIDs are also used in the acute pain caused by gout because they inhibit urate crystal phagocytosis besides inhibition of prostaglandin synthase.

**Antipyretic activity**

NSAIDS have antipyretic activity and can be used to treat fever. Fever is caused by elevated levels of prostaglandin HYPERLINK "https://en.wikipedia.org/wiki/Prostaglandin_E2"E2, which alters the firing rate of neurons within the hypothalamus that control thermoregulation. Antipyretics work by inhibiting the enzyme COX, which causes the general inhibition of prostanoid biosynthesis (PGE2) within the hypothalamus. PGE2 signals to the hypothalamus to increase the body's thermal set point. Ibuprofen has been shown more effective as an antipyretic than paracetamol (acetaminophen).Arachidonic acid is the precursor substrate for cyclooxygenase leading to the production of prostaglandins F, D & E.

**COX-2 inhibitors**

These drugs have been derived from NSAIDs. The cyclooxygenase enzyme inhibited by NSAIDs was discovered to have at least 2 different versions: COX1 and COX2. Research suggested most of the adverse effects of NSAIDs to be mediated by blocking the COX1 (constitutive) enzyme, with the analgesic effects being mediated by the COX2 (inducible) enzyme. Thus, the COX2 inhibitors were developed to inhibit only the COX2 enzyme (traditional NSAIDs block both versions in general). These drugs (such as rofecoxib,celecoxib, and etoricoxib) are equally effective analgesics when compared with NSAIDs, but cause less gastrointestinal hemorrhage in particular.

After widespread adoption of the COX-2 inhibitors, it was discovered that most of the drugs in this class increase the risk of cardiovascular events by 40% on average. This led to the withdrawal of rofecoxib and valdecoxib, and warnings on others. Etoricoxib seems relatively safe, with the risk of thrombotic events similar to that of non-coxib NSAID diclofenac.

**COX-2 inhibitor**

Selective COX-2 inhibitors are a type of non-steroidal anti-inflammatory drug (NSAID) that directly targets cyclooxygenase-2, COX-2, an enzyme responsible for inflammation and pain. Targeting selectivity for COX-2 reduces the risk of peptic ulceration, and is the main feature of celecoxib, rofecoxib and other members of this drug class. After several COX-2 inhibiting drugs were approved for marketing, data from clinical trials revealed that COX-2 inhibitors caused a significant increase in heart attacks and strokes, with some drugs in the class having worse risks than others. Rofecoxib (commonly known as Vioxx) was taken off the market in 2004 because of these concerns and celecoxib and traditional NSAIDs received boxed warnings on their labels.

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**Medical uses**

Some COX-2 inhibitors are used in a single dose to treat pain after surgery. Etoricoxib appears as good as if not better than other pain medications. Celecoxib appears to be about as useful as ibuprofen.

NSAIDs are often used in treatment of acute gout attacks. COX-2 inhibitors appear to work as well as nonselective NSAIDS. They have not been compared to other treatment options such as colchicine or glucocorticoids.

**Pharmacology**

**Opioid comparison**

| *Drug* | *Relative Potency* | *Nonionized Fraction* | *Protein Binding* | *Lipid Solubility* |
|---|---|---|---|---|
| *Morphine* | *1* | ++ | ++ | ++ |
| *Meperidine* | *0.1* | + | +++ | ++ |
| *Hydromorphone* | *10* | | + | +++ |
| *Alfentanil* | *10–25* | ++++ | ++++ | +++ |
| *Fentanyl* | *75–125* | + | +++ | ++++ |
| *Remifentanil* | *250* | +++ | +++ | ++ |
| *Sufentanil* | *500–1000* | ++ | ++++ | ++++ |
| *Etorphine* | *1000–3000* | | | |

*Opioids bind to specific opioid receptors in the nervous system and other tissues. There are three principal classes of opioid receptors, μ, κ, δ (mu, kappa, and delta), although up to seventeen have been reported, and include the ε, ι, λ, and ζ (Epsilon, Iota, Lambda and Zeta) receptors. Conversely, σ (Sigma) receptors are no longer considered to be opioid receptors because their activation is not reversed by the opioid inverse-agonist naloxone, they do not exhibit high-affinity binding for classical opioids, and they are stereo selective for dextroHYPERLINK "https://en.wikipedia.org/wiki/Dextrorotation"-rotatory isomers while the other opioid receptors are stereo-selective for levo-rotatory isomers. In addition, there are three*

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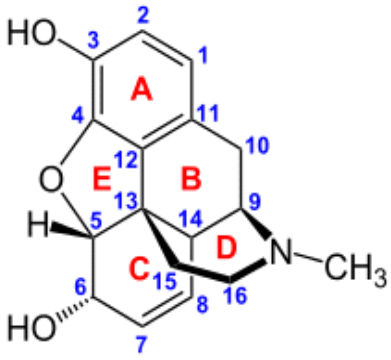
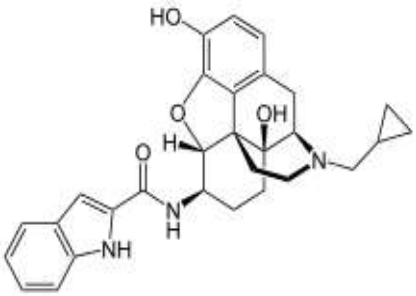
*subtypes of μ-receptor: $\mu_1$ and $\mu_2$, and the newly discovered $\mu_3$. Another receptor of clinical importance is the opioid-receptor-like receptor 1 (ORL1), which is involved in pain responses as well as having a major role in the development of tolerance to μ-opioid agonists used as analgesics. These are all G-protein coupled receptors acting on GABAergic neurotransmission.*




Locants of the morphine molecule

*The pharmacodynamics response to an opioid depends upon the receptor to which it binds, its affinity for that receptor, and whether the opioid is an agonist or an antagonist. For example, the supraspinal analgesic properties of the opioid agonist morphine are mediated by activation of the $\mu_1$ receptor; respiratory depression and physical dependence by the $\mu_2$ receptor; and sedation and spinal analgesia by the κ receptor[ Each group of opioid receptors elicits a distinct set of neurological responses, with the receptor subtypes (such as $\mu_1$ and $\mu_2$ for example) providing even more [measurably] specific responses. Unique to each opioid is its distinct binding affinity to the various classes of opioid receptors (e.g. the μ, κ, and δ opioid receptors are activated at different magnitudes according to the specific receptor binding affinities of the opioid). For example, the opiate alkaloid morphine exhibits high-affinity binding to the μ-opioid receptor, while ketazocine exhibits high affinity to κ receptors. It is this combinatorial mechanism that allows for such a wide class of opioids and molecular designs to exist, each with its own unique effect profile. Their individual molecular structure is also responsible for their different duration of action, whereby metabolic breakdown (such as N-*dealkylation) is responsible for opioid metabolism.




INTA: selective agonist of KOR-DOR and KOR-MOR heteromers. Does not recruit β-arrestin II. Antinociceptive devoid of aversion, tolerance, and dependence in mice.

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**Functional selectivity**

A new strategy of drug development takes receptor signal transduction into consideration. This strategy strives to increase the activation of desirable signalling pathways while reducing the impact on undesirable pathways. This differential strategy has been given several names, including functional selectivity and biased agonism. The first opioid that was intentionally designed as a biased agonist and placed into clinical evaluation is a chemical compound with the code number TRV130. It displays analgesic activity and reduced adverse effects.

**Opioid comparison**

Extensive research has been conducted to determine equivalence ratios comparing the relative potency of opioids. Given a dose of an opioid, an equianalgesic table is used to find the equivalent dosage of another. Such tables are used in opioid rotation practices, and to describe an opioid by comparison to morphine, the reference opioid. Equianalgesic tables typically list drug half-lives, and sometimes equianalgesic doses of the same drug by means of administration, such as morphine: oral and intravenous.

**Flupirtine**

Flupirtine is a centrally acting K+ channel opener with weak NMDA antagonist properties.. It is used in Europe for moderate to strong pain and migraine and its muscle-relaxant properties. It has no anticholinergic properties and is believed to be devoid of any activity on dopamine, serotonin, or histamine receptors. It is not addictive, and tolerance usually does not develop. However, tolerance may develop in single cases.

**Specific agents**

In patients with chronic or neuropathic pain, various other substances may have analgesic properties. Tricyclic antidepressants, especially clomipramine and amitriptyline, have been shown to improve pain in what appears to be a central manner. Nefopam is used in Europe for pain relief with concurrent opioids. The exact mechanism of carbamazepine, gabapentin, and pregabalin is similarly unclear, but these anticonvulsants are used to treat neuropathic pain with differing degrees of success. Anticonvulsants are most commonly used for neuropathic pain as their mechanism of action tends to inhibit pain sensation.

**Specific forms and uses:**

**Combinations**:

Analgesics are frequently used in combination, such as the Paracetamol and codeine preparations found in many non-prescription pain relievers. They can also be found in combination with vasoconstrictor drugs such as pseudoephedrine for sinus-related preparations, or with antihistamine drugs for allergy sufferers.

While the use of paracetamol, aspirin, ibuprofen, naproxen, and other NSAIDS concurrently with weak to mid-range opiates (up to about the hydrocodone level) has been said to show beneficial synergistic effects by combatting pain at multiple sites of

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action, several combination analgesic products have been shown to have few efficacy benefits when compared to similar doses of their individual components. Moreover, these combination analgesics can often result in significant adverse events, including accidental overdoses, most often due to confusion that arises from the multiple (and often non-acting) components of these combinations.

**Topical or systemic:-**

Topical analgesia is generally recommended to avoid systemic side-effects. Painful joints, for example, may be treated with an ibuprofen- or diclofenac-containing gel (The labeling for topical diclofenac has been updated to warn about drug-induced hepatotoxicity. capsaicin also is used topically. Lidocaine, an anesthetic, and steroids may be injected into painful joints for longer-term pain relief. Lidocaine is also used for painful mouth sores and to numb areas for dental work and minor medical procedures. In February 2007 the FDA notified consumers and healthcare professionals of the potential hazards of the use of topical anesthetics. These topical anesthetics contain anesthetic drugs such as lidocaine, tetracaine, benzocaine, and prilocaine in a cream, ointment, or gel.

**Psychotropic agents:-**

Tetrahydrocannabinol (THC) and some other cannabinoids, either from the Cannabis sativa plant or synthetic, have analgesic properties, although the use of cannabis derivatives is currently illegal in many countries. A recent study finds that inhaled cannabis is effective in alleviating neuropathy and pain resulting from, e.g., spinal injury and multiple sclerosis. Other psychotropic analgesic agents include ketamine (an NMDA receptor antagonist), clonidine and other $\alpha_2$-adrenoreceptor agonists, and mexiletine and other local anaesthetic analogues.

## METHODOLOGY

### PLANT COLLECTION AND EXTRACTION

- Collection and extraction of leafs
- Leafs of ***sida acuata*** tree were collected (500gm) and washed with water to clean dust and soil.
- It was weathered inside park overnight and shade dried the flowers.
- Dried materials were taken, crushed it to coarse powder.
- The materials were weighed and transfer in to a clean round bottom flask.
- Sufficient quantity of methanol was added till it totally immersed and maceration it for seven days.
- The extract was filtered by using muslin cloth.
- Mare was pressed and taken out and extraction procedure was repeated two more time with the same mare.
- The obtain filtrate was evaporated and cooled to dryness at $45^0$ to $55^0$c. Until it become like a semisolid.

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***Sida acuta* plant image**

**PHYTOCHEMICAL ANALYSIS**

Methanolic extract of ***sida acuata*** leafs were subjected to qualitative Phytochemical tests for different constituents such as alkaloids, carbohydrates, glycosides, flavonoids, Phenolic compounds, tannins, proteins and free amino acids, saponins, steroids and terpenoids.

**1. Test for alkaloids:**

Alkaloids were tested in three extracts, chloroform, ethanol and water. In chloroform extract, 10 mg of chloroform residue was macerated with HCL (2%). The resulting acid solution was filtered and filtrates were separately tested with alkaloidal reagents such as:

Dragendroffs reagent (Potassium bismuth iodide solution) Hager's reagent (A saturated solution of picric acid)

Mayer's reagent (Potassium mercuric iodide solution)

Wagner's reagent (Solution of iodine in potassium iodide)

In alcoholic extract, 10 mg of ethanol residue was macerated with HCI (2%), filtered,

Basified with $NH_4OH$ (25%) and extracted with $CHCL_3$. The chloroform soluble portion was evaporated, dissolved in HCL (2%) and tested as in the chloroform extract.

In water extract, 10 mg of aqueous residue was dissolved in distilled water (1.5 ml), basified with $NH_4OH$ (25%) and extracted with $CHCL_3$. The chloroform soluble portion was extracted with HCI (10%) and the aqueous acid solution tested as in the chloroform extract.

**2. Test for Carbohydrates:**

Small quantity of water extracts was dissolved separately in 5 ml of dissolved water and filtered.

**Molisch test:**

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The filtrate was treated with few drops of α-naphthol (20% in ethyl alcohol). Then about 1 ml of concentrated $H_2SO_4$ was added along the sides of inclined test tube and observed for formation of violet colored ring at the interface.

**3. Test for glycosides and anthraquinones:**

**Borntrager's test:**

A small amount of ethanol and water extracts was separately hydrolyzed with hydrochloric acid for few hours on a water bath and the hydrolyzed was extracted with benzene. The benzene layer was treated with dilute ammonia solution and observed for the formation of reddish pink color.

**Legal test:**

The extracts were dissolved in pyridine and made alkaline with few drops of 10% NaOH and then freshly prepared sodium nitroprusside was added and observed for formation of blue color.

**4. Test for flavonoids:**

**Ammonia test:**

Filter paper atrips were dipped in the dilute solution of various extracts, ammoniated and observed for color changes from white to yellow.

**5. Test for Tannins and Phenolic compounds:**

The water and ethanol extracts (10 mg each) were dissolved in distilled water. The water and ethanol extracts were then separately dissolved into three parts. A sodium chloride (10%) solution was added to one portion of each test extracts, 1% gelatin solution to each second portion and the gelatin salt reagent to each third portion. Precipitation with the latter reagent or with both the gelatin salt reagents was indicative of the presence of tannins. Precipitation with the salt solution (Control) indicated a false-positive test. Positive testes were further confirmed by the addition of a few drops of dilute ferric chloride (1% $FeCl_3$) to the test extracts, which gave blue black or green black coloration.

**6. Test for Protiens and Aminoacids:**

Small amount of ethanol and water extracts were dissolved in distilled water and filtered.

**Biuret's test:**

To the ammoniated alkaline filtrates, added 2-3 drops of 0.002% copper sulfate and observed for appearance of red or violet color.

**Millon's test:**

To 2 ml of filtrate, 5-6 drops of millons reagent (1g of mercury + 9 ml of fuming nitric acid solution) were added and observed for red precipitates.

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**Ninhydrin test:**

To the filtrate, lead acetate solution was added to precipitate tannins and filtered. The filtrate was spotted on a paper chromatogram, sprayed with ninhydrin reagent and heated at 110 C for 5 minutes and observed for red or violet color.

**Xanthoprotien test:**

To the filtrate, a few drops of concentrated nitric acid was added by the sides of the test tube and observed for appearance of yellow color.

**7. Test for Saponins:**

**Foam test:**

A small amount of various extracts were extracted with petroleum ether and acetone. To the insoluble residue left after extraction, a few ml of water was added and shaken vigorously for 15 minutes and observed for formation of honeycomb froth that persisted for at least 30 minutes.

**8. Test for Sterols and or Triterpenes:**

The extracts were refluxed with alcoholic potassium hydroxide until the saponification was complete. The saponification mixture was diluted with distilled water and extracted with diethyl ether. The ethereal extract was evaporated and the unsaponifiable matter was subjected to following tests.

**Libermann-Burchard's test:**

The ether soluble residue was dissolved in chloroform and few drops acetic anhydride was added followed by few drops of concentrated sulphuric acid from the sides of the test tube and observed for the formation of blue to blue-red color.

**Salkowski's reaction:**

To the ether soluble residue, 2 ml of concentrated sulphuric acid was added and observed for the formation of yellow ring at the junction, which turns red after one minute**.**

**EXPERIMENTAL DEGINE**

**Animals**

A total of 25 Wistar albino rats of either sex weighing 150-250 g were used for hot plate method. All the animals were obtained from the Animal house, Department of Pharmacy, Dr CSN institute of pharmacy, Bhimavaram. All the animals received standard laboratory diet, reverse osmosis water.

**PREPARATION OF DRUG SAMPLE:**

The extract was suspended in distilled water and it is used for the analgesic study.

**REFERENCE DRUG**:

Diclofenac Sodium (10mg/kg) was prepared by dissolving them in normal saline at concentration of 15mg/ml.

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**EDDY'S HOT PLATE METHOD**

The analgesic activity was evaluated by the Eddy's hot plate method. All Formulations for analgesic activity were administered orally. The standard drug Diclofenac sodium was administered in the form of solution in water for injection as vehicle. For the assessment of analgesic activity the animals five were divided into five groups each composed of five animals. All groups received intraperitoneal injection (maximum 1 ml as per ethical norms).

The animals were divided into five groups of 5animals each
**Group I** served as control.
**Group II** served as standard and was injected Diclofenac sodium (9 mg/kg) intraperitoneal.
**Group III** served as extract low dose 100 mg/kg and
**Group IV** served as extract at high dose 200 mg /kg

The animals were individually placed on the hot plate maintained at 55°C, one hour after their respective treatments. The response time was noted as the time at which animals reacted to the pain stimulus either by paw licking or jump response, whichever appeared first. The cut off time for the reaction was 15 seconds.

| S.NO | GROUPS | DOSE |
|---|---|---|
| 1 | I | Cnotrol |
| 2 | II | Standard (diclofenac 10 mg/kg) |
| 3 | III | Extract low dose 100 mg/kg |
| 4 | IV | Extract high dose 200 mg/kg |

**EVALUTION OF ANALGESIC ACTIVITY**

Evaluation of analgesic activity of the extract was also carried out using hot plate method. The rats were placed on a hot plate maintained at 55°C within the restrainer. The reaction time (in seconds) or latency period was determined as the time taken for the rats to react to the thermal pain by licking their paws or jumping. The reaction time was recorded before (0 min) and at 15, 30, 45, and 60 min after the administration of the treatments. The maximum reaction time was fixed at 45 sec to prevent any injury to the tissues of the paws. If the reading exceeds 45 sec, it would be considered as maximum analgesia. The maximum possible analgesia (MPA) was calculated as follows:

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## RESULTS

### PHYTOCHEMICAL STUDY OF METHANOLIC EXTRACT OF *SIDA ACUTA*

| S. No | Class of compound | Plant part (leaf) | Test performed |
|---|---|---|---|
| 1 | Alkaloids | + | Dragendorff's test, Mayers test |
| 2 | Carbohydrates | + | Molish test, Fehling test |
| 3 | Glycosides | + | Keller killiani test |
| 4 | Phenolic compounds / tannins | + | Ferric chloride test |
| 5 | Proteins and amino acids | + | Xantho protein test |
| 6 | Flavonoids | + | Ammonia test |
| 7 | Saponins | + | With water With Na2CO3 |
| 8 | Sterols | + | Liebermann-Burchard test, Salkowski reaction, Hesse's reaction |
| 9 | Acid compounds | + | With Na2CO3, With litmus paper |
| 10 | Resins | + | With double distilled water, With acetone and conc. HCl |
| 11 | Peroxides | - | Potassium Iodide test |
| 12 | Polyuronoids | - | Haemotoxylin test |

### Evaluation of analgesic activity of methanolic extract of sida *acuta* on rats by using Eddy's Hot plate method

| Treatments | Reaction Time in Seconds (Mean ± SEM) | | | | |
|---|---|---|---|---|---|
| | 0 Mins | 15 Mins | 30 Mins | 45 Mins | 60 Mins |
| Control | 4.25 ± 0.57 | 4.50 ± 0.34 | 4.42 ± 0.45 | 4.58 ± 0.44 | 5.17 ± 0.80 |
| Standard | 11.04±0.73$^{*ab}$ | 11.92±0.84$^{*ab}$ | 12.83±0.35$^{*ab}$ | 13.33±0.83$^{*ab}$ | |
| Dil$^{n}$(10mg/ kg) | 6.50 ± 1.22 | 5.29 ± 0.57 | 6.75 ± 0.62*$^{a}$ | 5.75 ± 0.56 | 6.79 ±1.24 |
| Extract low(100mg/kg) | 4.13 ± 0.54 | 7.04 ± 0.67$^{a}$ | 8.04 ± 0.73$^{a}$ | 9.00 ± 0.92$^{a}$ | 9.67 ± 0.86 |
| Extract high(200mg/kg) | 6.67 ±0.85$^{a}$ | | | | |

All values by Student's t-test , significant at P <0.005, and SEM = standard error mean . *P<0.05 versus baseline of the respective treatment $^{a}$p<0.05treatment versus control,$^{b}$p<0.05 extract versus morphine sulfate, extract versus sodium salicylate was not significant at all-time points.

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## DISCUSSION

Analgesics are drugs that act on peripheral or central nervous system to selectively relieve pain without significantly altering consciousness. Centrally acting analgesics act by raising the threshold for pain and also altering the physiological response to pain. On the other hand, peripherally acting analgesics act by inhibiting the generation of impulses at chemoreceptor site of pain. The animal models employed for screening of analgesic activity in this study are pain-state models using thermal stimuli which include tail-flick and hot plate methods. Both methods are useful in illustrating centrally mediated antinociceptive responses which focus generally on changes above the spinal cord level. While the tail-flick method mediates a spinal reflex to a nociceptive stimulus, hot plate method involves higher brain functions and is regarded a supraspinally organized response

The methanol extract from the leafs of *Sida acuta* increase the reaction time of the rats on hot plate method in this study. The difference in the mean reaction time of the extract and the control groups was statistically significant during all observation times. Analgesia in Dclofenac treated rats was detectable at 45 and 60 min. Significant analgesic effect was observed between control and the extract tested. Hot plate method produces two measureable behavioural components in response to thermal pain, with regard to their reaction times. Responses such as paw licking and jumping in rats are considered to be supraspinally integrated. Thus, the extract to shows these behaviors on hot plate method indicates that it might be acting at supraspinal level.

## CONCLUSION

In conclusion, the methanol extract of the *Sida acuta* displayed analgesic activity and supported the traditional use of this plant in pain relief. Further study is warranted to identify the active compounds present in this extract and to elucidate the mechanisms involved in its analgesic properties.

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