Nat. Volatiles & Essent. Oils, 2021; 8(4): 4017-4039

NVEO
Natural Volatiles & Essential Oils

# Evaluation of ethanolic extract of Citrulluslanatus seeds for analgesic and anti-pyretic activity in animal model

**Krupavaram. B[a], Kogila A/P Subramaniama[a], Long Chiau Ming[b], Tan Ching Siang[a], Bama V.V Menon[a], Anandarajagopal K[a], H. Jaasminerjiit Kaur[a], Shashidharan Menon[a], Abdullah Khan[a], Liew Kai Bin[c*]**

[a] Centre of Excellence in Pharmaceutical Sciences, School of Pharmacy, KPJ Healthcare University College, Lot PT 17010, PersiaranSeriemasUtama, Kota Seriemas, 71800 Nilai, Negeri Sembilan, Malaysia.

[b] PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Gadong, Brunei Darussalam.

[c]Faculty of Pharmacy, University of Cyberjaya, PersiaranBestari, 63000 Cyberjaya, Selangor, Malaysia

*email : Dr. Liew Kai Bin University of Cyberjaya Faculty of Pharmacy Persiaran Bestari, 63000 Cyberjaya, Selangor, Malaysia

**ABSTRACT**

**Objective:** This currentstudy was design to identify the effect of analgesic and antipyretic activity for ethanolic seed extract of Citrulluslanatus seeds.

**Methodology:** The study was carried out using Sprague-Dawley rats (250-300g) and Albino mice (25-30g). Tramadol and Paracetamol are the standard drugs, was prepared by dissolving in distilled water to make the concentration of 20mg/kg and 150mg/kg for analgesic and antipyretic activity respectively.The effect of ethanolic extract of Citrulluslanatus seeds was investigated for analgesic activity through tail immersion method and for antipyretic activity through yeast induced pyrexia method

.**Results:** The analgesic activity was evaluated using tail immersion method in mice.The ethanolic extract of Citrulluslanatus seeds was shown highly significant ($p<0.001$) analgesic activity at high dose which is almost comparable to standard drug and at low dose (200 mg/ kg) showed less significant ($p<0.05$) analgesic activity. In antipyretic activity, the ethanolic extract of Citrulluslanatus seeds was shown highly significant ($p<0.001$) at high dose and at low dose (200 mg/ kg) respectively.The ethanolic extract of Citrulluslanatus seeds in both low and high dose showed highly significant at 4th hour which is almost comparable to standard drug.

**Conclusion:** The findings of the present study concluded that Citrulluslanatusseeds have potential to treat pain and fever and as a good source, novel natural analgesic and antipyretic agents. The ethanolic extract ofCitrulluslanatusseeds showed highly significant analgesic and antipyretic activity in mice and rats respectively.

**Keywords:** Citrulluslanatus, Analgesic, Antipyretic, Ethanolic seed extract, Tailimmersion and Yeast induced pyrexia test.

**INTRODUCTION**

Pyrexia, often known as fever, is defined as a rise in the body's core temperature above the normal range of 36.5°C to 37.5°C due to an increase in the body's temperature regulation set point. As a result of invading bacteria, the body temperature rises.When macrophages are exposed to bacteria or other foreign substances, they emit pyrogens, which operate on the brain's temperature regulating centre, causing the temperature to rise. The hypothalamus, a tiny gland in the brain, is responsible for transmitting signals to the body's heating and cooling processes.

Antipyretics are substances or treatments that lower the body's temperature when it is too high. Body temperature regulation necessitates a careful balance between heat production and loss, as well as the hypothalamus, which controls body temperature set points. The most common antipyretic medicines include paracetamol, ibuprofen, acetaminophen, and acetylsalicylic acid. Antipyretic medicines reduce fever by reducing prostaglandin synthesis in the brain or by reducing the rise of interleukin-1 production after interferon generation.

Pain is part of the body's defence system, causing a reflexive recoil from the painful stimuli as well as tendencies to protect the injured body part while it heals and avoid a potentially dangerous scenario in the future. In addition to real or potential tissue damage, pain is an unpleasant sensory and emotional experience.When a signal is conveyed by nerve fibres to the brain for interpretation, we experience pain. Pain can be short-term or long-term, and it can be localised or diffuse across the body. Nociceptive pain and neuropathic pain are two types of pain.

Analgesics are pain relievers that work on the peripheral or central nerve systems to reduce pain selectively without affecting consciousness. Peripherally acting analgesics work by preventing impulses from being generated at the chemoreceptor location of pain. Synthetic analgesics and natural analgesics are the two forms of analgesics. Paracetamol, Ibuprofen, COX-2 inhibitors, NSAIDs, diclofenac, and many other synthetic medicines with analgesic effect are available on the market. Analgesic medications operate by inhibiting substances called prostaglandins, which stimulate peripheral pain receptors and cause them to convey pain signals to the brain (CNS).

The water melon, Citralluslanatus, produces a fruit that is around 93 percent water. The word "melon" originates from the fact that the fruit is huge and round, with a delicious, pulpy interior. The watermelon's scientific name is drawn from both Greek and Latin

roots. Citrullus is derived from the Greek word "citrus," which refers to the fruit.The word lanatus comes from the Latin word lanatus, which means woolly, and refers to the plant's tiny hairs on the stems and leaves(Baker, et al.,2012).

Citralluslanatus seeds are prized for their unique characteristics and medicinal properties. The pharmacodynamic response of CitrullusLanatus seeds is elicited by a complex interaction of chemical components. Total phenol concentration is highest in seeds, followed by flavanoids, and lowest in tannis(Gupta Alkaet al.,2018).

In the present study, we have chosen a plant Citralluslanatusseeds, which is a very popular medicinal agent in ethnic medicine. However, there is no scientific data on the usage of Citralluslanatus seeds for analgesic and antipyretic properties in complete plants.Hence, this topic has been chosen to evaluate whether does Citralluslanatusseeds has the ability to empower analgesic and anti-pyreticactivity.

**METHODOLOGY**

**COLLECTION OF PLANTMATERIAL**

The Citrulluslanatusis in flower from July to August. The species is monoecious and is pollinated by Insects. The plant is self-fertile. The 1 kg of Citrulluslanatusseed were collected from the fruit store available in Petaling Jaya, Selangor. The collected plants was carefully examined and authenticated by a Pharmacognosist from University Putra Malaysia, Serdang, Selangor Darul Ehsan, Malaysia. The Citrulluslanatusseeds were identified by Dr. Mohd. Firdaus Ismail in Biodiversity Unit in the Institute of Bioscience, University Putra Malaysia. The specimen representing this collection has been deposited in the Herbanium of Institute of Bioscience, University Putra Malaysia, for further reference

**PREPARATION OFMATERIAL**

Citrulluslanatus seeds were collected and washed well with tap water before being rinsed with sterile water. The seeds were first dried in the shade for four weeks at room temperature before being pulverised. Using a dry grinder, the dried seed was reduced in size to a coarse product and passed through size no: 30 before being kept in a firmly sealed container.The cold maceration method was used to extract ethanol from fresh coarse powder. Using 500ml of ethanol, 250g of coarse powder was extracted using a cold maceration technique. The sample was soaked for seven days and violently shaken three times a day at the appropriate intervals.The extraction was filtered using

Whatman no. 1 filter paper and dried with a rotary evaporator (below 50%), then stored in a firmly sealed container in a dry place.

**PELIMINARY PHYTOCHEMICALSCREENING**

The preliminary phytochemical screening was conducted for the extract ofCitrulluslanatusseeds using suitable methodologies to identify the presence of plant secondary metabolites such as alkaloids, carbohydrates, and glycosides, protein and amino acids, oils and fats, saponins, terpenoids, flavonoids, sterols, phenolic compounds, tannins as well as gums and mucilages.

**COLLECTION OR SELECTION OFANIMALS**

Healthy Sprague-Dawley rats weighing about (250-300g) and Albino mice weighing about (25-30g) of either sex and age were procured from the animal house at the KPJ Healthcare University College (KPJUC), Nilai, and were kept under standard husbandry conditions. During the investigation, the animals were fed regular laboratory diet.The animal was maintained under temperature ($22^0C \pm 3$), humidity ($60 \pm 5\%$) and a 12 hour light and dark cycle.The experimental protocol has been approved by KPJUC institutional Animal Ethical & Committee (IAEC). KPJ Healthcare University College, Nilai, Negeri Sembilan, Malaysia. (Reference No. KPJUC/RMC/BPS/EC/2018/154) dated on 18$^{th}$ September 2018.

**Study on Anti-pyretic activities**

Five groups of Sprague-Dawley rats (n=6) will be formed. Each rat's normal body temperature will be measured rectally using a thermometer at one-hour intervals and recorded. Brewer's yeast-induced pyrexia in Sprague-Dawley rats will be used to test the extract's antipyretic properties. A subcutaneous injection of 15 percent w/v yeast suspended in methyl cellulose solution was given to the animals.The vehicle, standard medicine, and test drug were given to different groups 18 hours after the yeast injection. The control group of animals will be given normal saline, whereas the standard group will be given 150 mg/kg of paracetamol.The ethanol extract of Citralluslanatus seeds will be given orally to two groups of mice at doses of 200 mg/kg and 400 mg/kg of body weight, respectively. The rectal temperature will be taken with a clinical thermometer at 0, 30 minutes, 1, 2, and 3 hours after the medicine has been administered and tabulate the reading in the table. (Shaik. Karimulla et.al, 2015)

**Study on Analgesic activities**

Before the experiment, the mice were separated into four groups (n=6) and fasted for 12 hours. The tail immersion method was used to test the analgesic activity of several Citralluslanatus seed extracts. Each mouse was weighed accurately before any treatment, and the tail immersion reading was recorded for each mouse.The group Igiven orally normal saline 1 % serve as a control.Groups II were given standard drugs Tramadol respectively (20 mg/kg) was administered orally, half an hour before the screening. The ethanol extract of Citralluslanatus seeds was given orally 200mg/kg as low dose to group III and group IV received ethanol extract of Citralluslanatus seeds 400mg/kg as high dose, one hour before start the tail immersion method. Placing the mice tail up to 1-2 cm into the beaker of hot water which maintained at ($55^0C\pm 0.5$). The time it took the mice to withdraw their tails from the hot water was recorded as the response time; the cut off time for tail immersion was set at 15 seconds, and the response was recorded at 0, 30, 60, 90, and 120 minutes after administration of the extract and standard drug. (S.K Sharma et al.,2004)

**Statistical analysis**

SPSS software was used to carry out statistical analysis of the data. All the values were expressed as mean ± standard error of mean. One-way ANOVA test was used to calculate the mean differences and followed by Dunnett's test for multiple comparisons. Value of P less than 0.05 was considered significant while P value less than 0.01 was considered highly significant.

**RESULTS**

**Preliminary phytochemical analysis**

Based on preliminary phytochemical screening conducted, both analgesic and anti-inflammatory activity with ethanolic extract of Citrulluslanatus seeds showed the presence of alkaloids, carbohydrates, and glycosides, phenolic compound, and tannins, flavonoids, volatile oil and terpenoids.

**Result of Anti-pyretic activity**

Yeast induced pyrexia was used to test the antipyretic effect of Citrulluslanatus seeds extract. The antipyretic effect of an ethanolic extract of Citrulluslanatus seeds on Sprague Dawley rats weighing 200 - 250 g/kg by weight.A subcutaneous injection of Brewer's Yeast in distilled water raised the fever.The ethanolic seed extracts at 200 mg/kg and 400 mg/kg were given orally for 18 hours following the Brewer's yeast injection. The Paracetamol 150 mg/kg tablets were used as standard drug. The mean increase in fever was measured using digital thermometer at 0 hours, 30 minute, 1 hour, 2 hours, 3 hours, 4 hours, and $5^{th}$ hour after the administration of seed extract and standard drug in each

rat. The $0^{th}$-hour reading considered as the initial fever of the animal. In the present study, the ethanolic extracts exhibited a reduction in temperature induced by yeast.

Table 4.3: The antipyretic activity of Citrulluslanatusethanolic seed extracts in experimental Sprague Dawley rats (n=6).

| Group | Initial rectal temperature before yeast injection ($^0$ C) | Rectal temperature after 18 hours of yeast injection ($^0$ C) (0 hour) | Rectal temperature after administration of extract ($^0$C) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 1/2 hour | 1 hour | 2 hour | 3 hour | 4 hour | 5 hour |
| Normal Control | 33.85 ± 0.44 | 36.10 ± 0.15 | 36.95 ± 0.16 | 37.35 ± 0.14 | 38.10 ± 0.18 | 38.55 ± 0.13 | 38.88 ± 0.09 | 39.38 ± 0.13 |
| Standard Control Paracetamol (150mg/kg) | 34.05 ± 0.68 | 37.45 ± 0.18 | 37.73 ± 0.20 | 36.83 ± 0.25 | 36.35 ± 0.21 ** | 36.10 ± 0.18 *** | 35.45 ± 0.16 *** | 34.83 ± 0.11 *** |
| Citrulluslanatus (200 mg/kg) | 33.18 ± 0.34 | 37.43 ± 0.09 * | 36.93 ± 0.19 | 36.45 ± 0.21 | 36.18 ± 0.21 | 36.90 ± 0.13 ** | 36.43 ± 0.19 *** | 35.68 ± 0.20 *** |
| Citrulluslanatus (400 mg/kg) | 33.53 ± 0.08 | 36.55 ± 0.16 | 37.60 ± 0.11 * | 37.23 ± 0.18 | 37.00 ± 0.13 | 36.80 ± 0.20 *** | 36.33 ± 0.19 *** | 34.93 ± 0.85 *** |

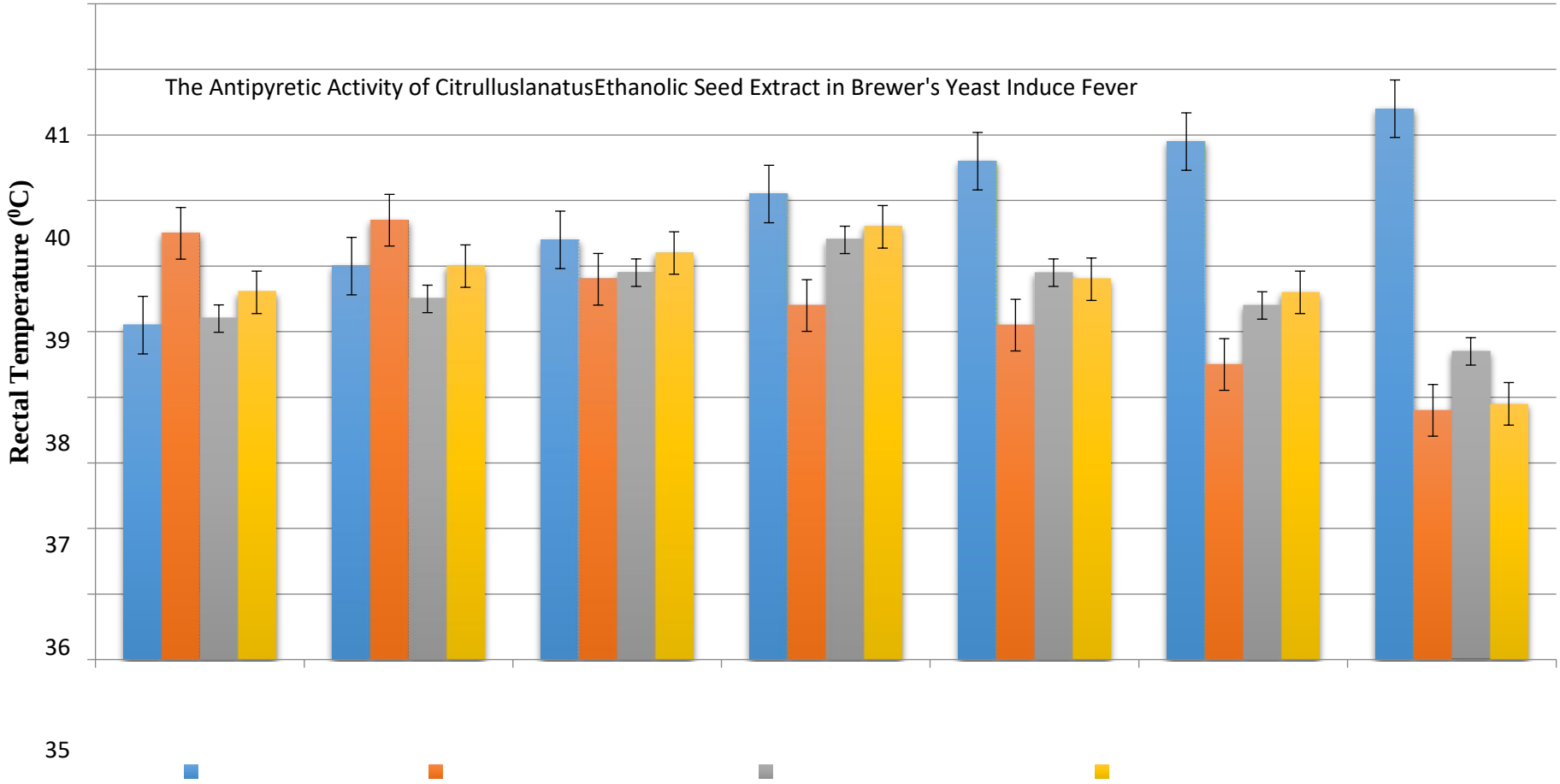
Values are expressed as Mean ± SEM. n = 4 in each group, * indicated $p < 0.05$, ** indicate $p < 0.01$ and *** indicate $p < 0.001$ compared to normal control.

Table 4.3 shows the activity of ethanol extract of Citrulluslanatusseeds on yeast induced pyrexia. The rectal temperature of the rats were noted at 30 minute, 1, 2, 3, 4, and 5$^{th}$ hour after the administration of drug treatment. The experimental rats showed an increased in the rectal temperature after 18 hours of Brewer's yeast injection. The body temperature of the rats was reducing by treating with the extracts at dose of 200 mg/kg and 400 mg/kg and Paracetamol at dose of 150 mg/kg body weight.

The antipyretic activity of the extract at dose of 200 mg/kg started to show the effect from 2$^{nd}$ hour onwards and continued to reduce until 5$^{th}$ hour. Moreover, the treatment with the extracts of dose 400mg/kg body weight exhibited its effect at 1st hour and continued to decrease until 5th hour after the administration of the extract. The treatment with standard drug (Paracetamol 150mg/kg) showed reduction in the rectal temperature from 30 minute. The higher dose (400 mg/kg of Citrulluslanatus seed) has better activity at the5th hour which is almost comparable to the standard drug.

Thus, anti-pyretic activity of Citrulluslanatus seeds at the dose of 200 mg/kg was less significant ($p < 0.05$) at the 2nd hour. The activity increased at the 3rd hour, 4th and 5th hour and was highly significant ($p < 0.001$) at the dose 400 mg/kg. The anti - pyretic was comparable to the Paracetamol (standard drug) at a dose of 150 mg/kg. The outcomes for both extracts treated groups and standards were compared with normal control group.

Figure 4.1: The antipyretic activity of Citrulluslanatusethanolic seed extracts in experimental Sprague Dawley rats (n=6).



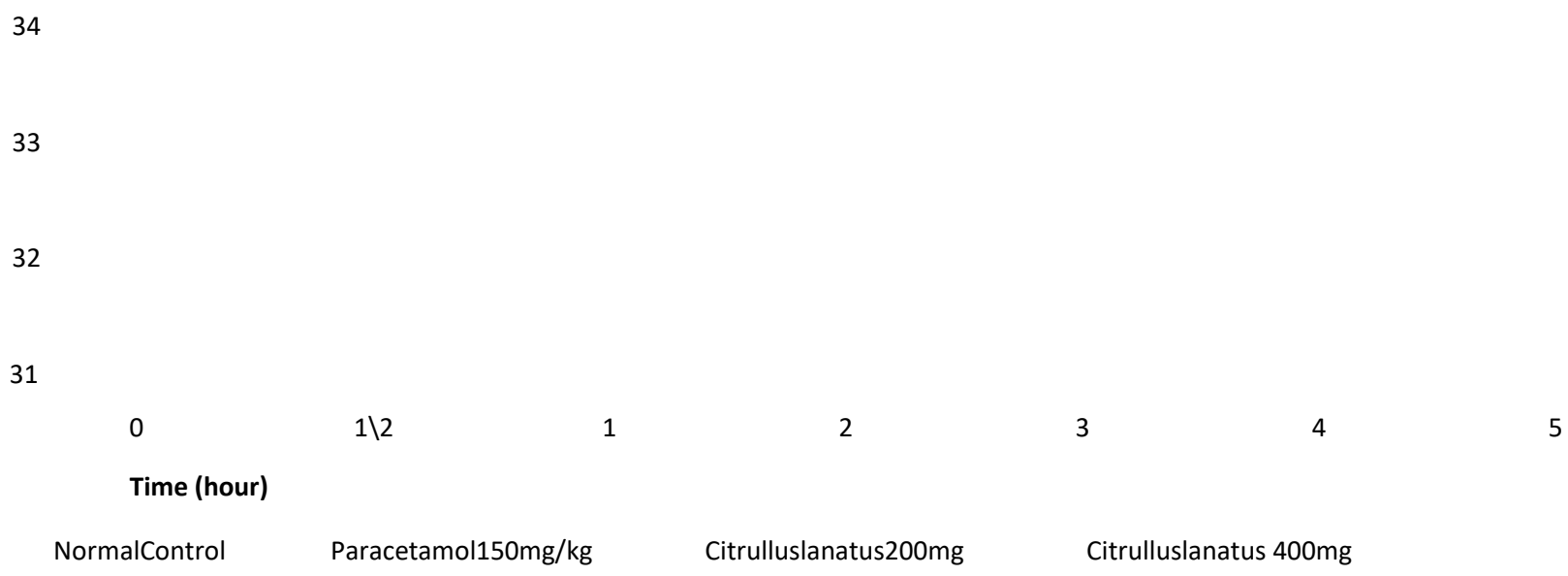
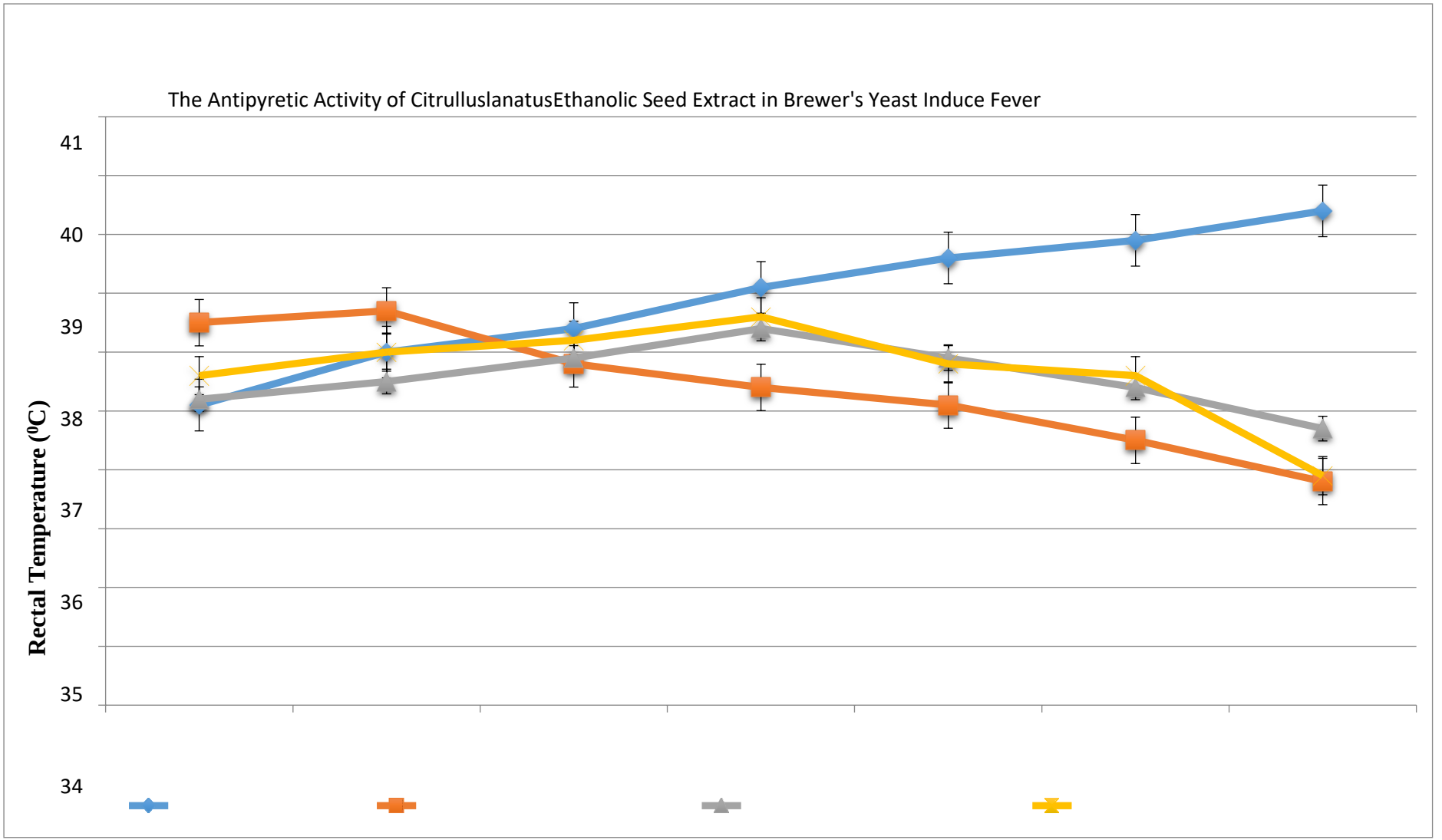
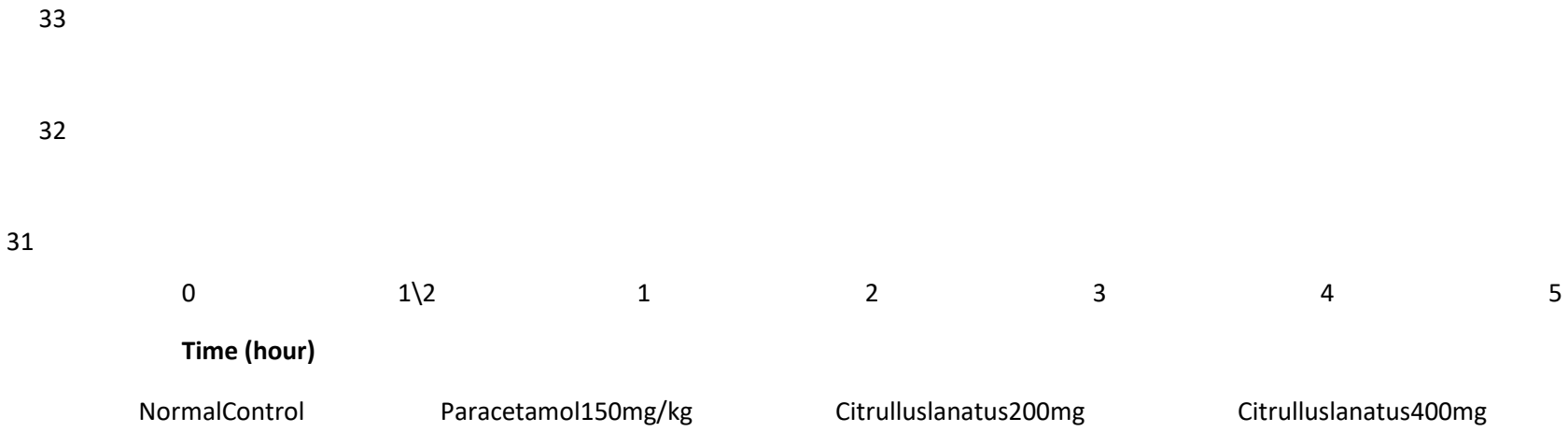

34
33
32
31
0
1\2
1
2
3
4
5
Time (hour)
NormalControl
Paracetamol150mg/kg
Citrulluslanatus200mg
Citrulluslanatus 400mg

Figure 4.2: The antipyretic activity of Citrulluslanatusethanolic seed extracts in experimental Sprague Dawley rats (n=6).




33
32
31
0
1\2
1
2
3
4
5
Time (hour)
NormalControl
Paracetamol150mg/kg
Citrulluslanatus200mg
Citrulluslanatus400mg

**ANALGESICACTIVITY**

The analgesic activity of Citrulluslanatusethanolic seeds extract on Swiss Albino mice were studied at the concentration of 25 mg/kg body weight. The treatment with the standard drug used was Tramadol 20 mg/kg were administered by intra peritoneal injection for 30 minute before starting of the tail immersion method. Followed by the Citrulluslanatusethanolic seeds extract of low dose (200 mg/kg) and high dose (400 mg/kg) were given orally 30 minute before starting of the tail immersion method. The low dose as well as high dose significantly showed analgesic activity, which increase the response time to the mice, whereas high dose shows good significant compare to low dose which is almost comparable to the standard drug. In the present study, both extracts exhibited the increases in the response time of themice.

The response of tail flick or withdrawals of the mice's were noted at 30, 60, 90, and 120 minutes after the administration of drug treatment. The response time of the mice were increased by treating with the extracts at dose of 200 mg/kg and 400 mg/kg and Tramadol at dose of 20 mg/kg body weight. The experiment as showed in Table 5.4 stated that the extract exhibited its action in doses of 200 mg/kg and 400 mg/kg from 60 minute of administration of Citrulluslanatus. The effect of ethanolic extract of Citrulluslanatuson the tail immersion method at different minute of study was compared to that of normal control for the evaluation of analgesicactivity.

Table 4.4: The analgesic activity of Citrulluslanatusethanolic seed extracts in experimental Swiss Albino mice (n=6).

| Treatment | Initial time | Reaction Time in Seconds ( MEAN ± SEM) | | | |
|---|---|---|---|---|---|
| | | 30 MIN | 60 MIN | 90 MIN | 120 MIN |
| Normal Control | 2.88 ± 0.43 | 2.85 ± 0.43 | 2.87 ± 0.41 | 2.82 ± 0.41 | 2.82 ± 0.43 |
| Standard Drug Tramadol 20mg/kg | 2.59 ± 0.30 | 6.50 ± 0.60*** | 5.68 ± 0.30*** | 5.33 ± 0.27*** | 6.25 ± 0.23*** |
| Citrulluslanatus 200mg/kg | 2.04 ± 0.26 | 2.51 ± 0.34 | 5.15 ± 0.27* | 2.86 ± 0.24 | 2.19 ± 0.16 |
| Citrulluslanatus 400 mg/kg | 3.35 ± 0.43 | 2.56 ± 0.43 | 5.42 ± 0.11*** | 6.34 ± 0.12*** | 7.30 ± 0.10*** |

Values are expressed as mean ± SEM (n = 6), less significant at * ($p<0.05$), significant at ** ($p<0.001$) and high significant at *** ($p<0.0001$) when compared to normal control and Citrulluslanatusethanolic seed extract.

The analgesic action of the extract at dose of 200 mg/kg shows the effect at 60 minute and this explained that the analgesic activity of the extract of the dose 200 mg/kg is less significant. Whereas the treatment with the extracts of dose 400mg/kg initially exhibited its effect at 60 minute and continued to increase until 120 minute after the administration of the extract. Meanwhile, the treatment with standard drug (Tramadol 20 mg/kg) showed increase in the tail flick or withdrawal time of the mice from 30 minute and continued to increase until the 120 minute. This reveals that the higher dose (400 mg/kg) of Citrulluslanatusseed has better activity from the 60 minute to 120 minute which is almost comparable to the standard drug Tramadol 20 mg/kg.

Thus, it can be concluding that at the 60 minute, the analgesic action of the Citrullulanatusseeds (200 mg/kg) was less significant ($p < 0.05$). Besides that, Citrulluslanatusseeds show highly significant ($p < 0.001$) at the dose 400 mg/kg at the $60^{th}$, $90^{th}$, and $120^{th}$ minute. The analgesic activity was comparable to the Tramadol (standard drug) at a dose of 20 mg/kg. The outcomes for both extracts treated groups and standards were compared with normal controlgroup.

Figure 4.3: The analgesic activity of Citrulluslanatusethanolic seed extracts in experimental Swiss Albino mice (n=6).

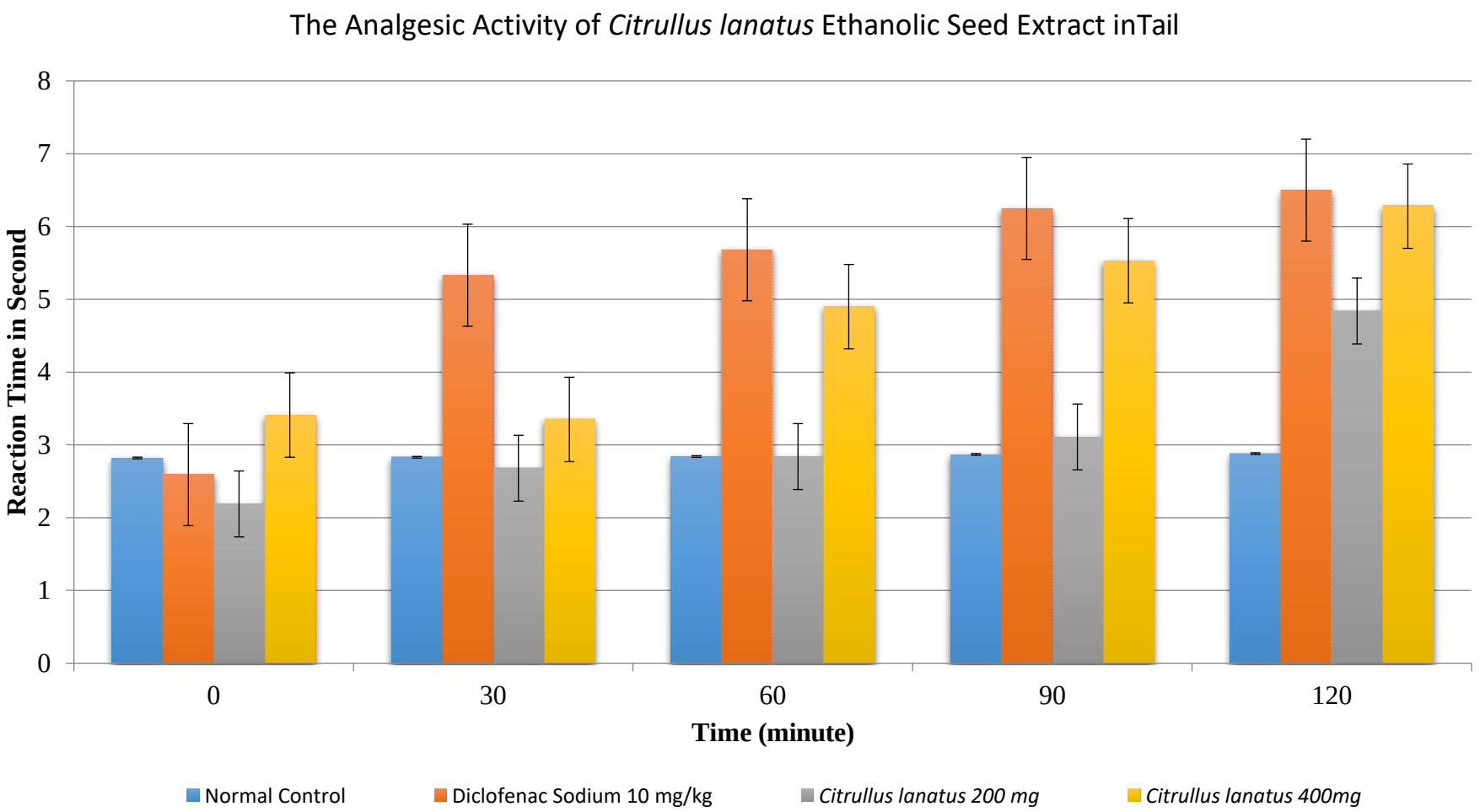
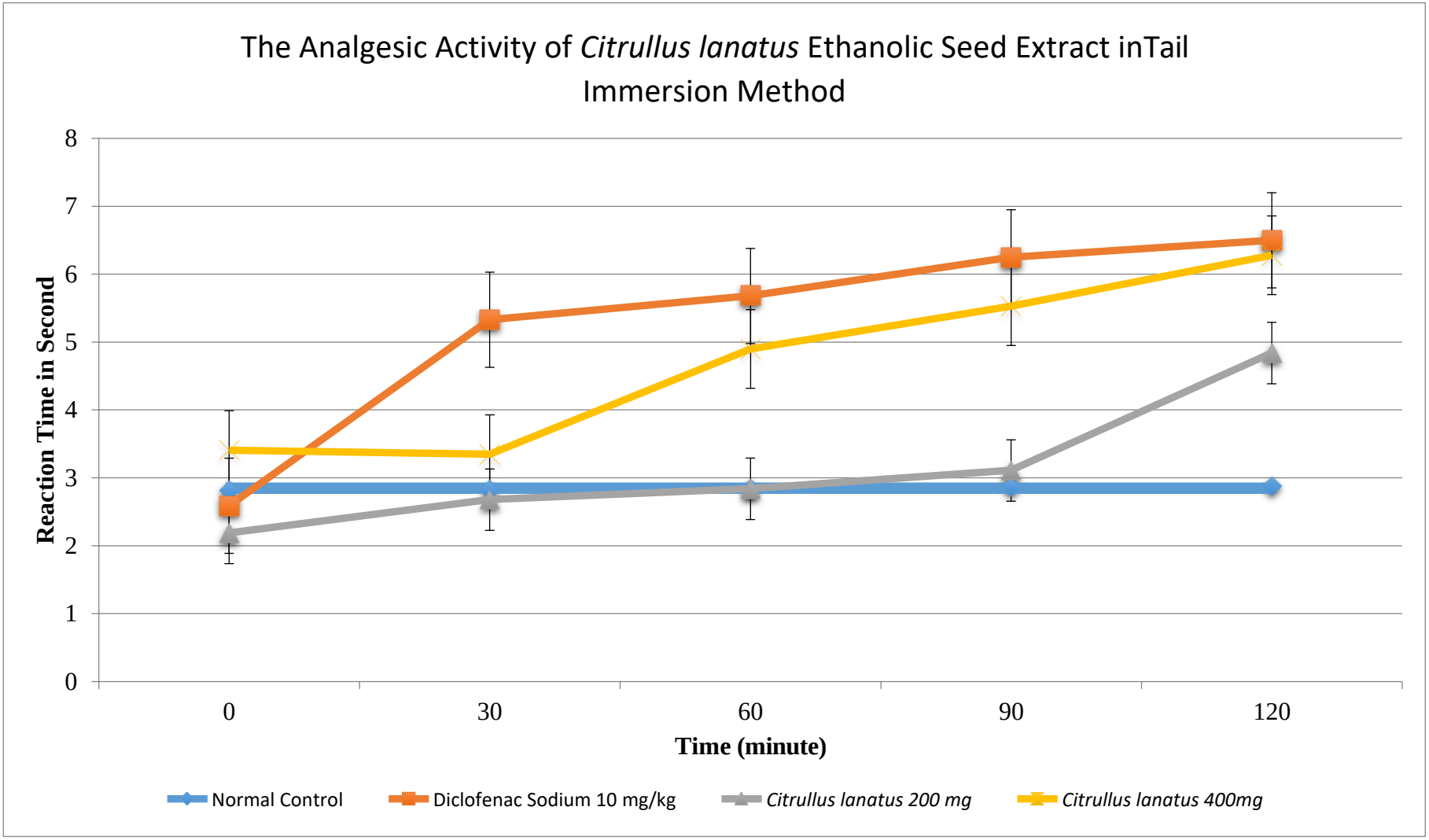


Figure 4.4: The analgesic activity of Citrulluslanatusethanolic seed extracts in experimental Swiss Albino mice (n=6).



**DISCUSSION**

Phytochemicals are plant components that play an important role in plant defence against animals, microbes, and have been used as medications for centuries. As a result, phytochemical screening is the initial step in anticipating the types of potentially active molecules that plants may produce(Chew et al., 2011). Preliminary phytochemicals analysis is a necessary step in determining the existence of significant phytoconstituents in medicinal plants that are responsible for the medical plant's specific activity (Manjulikaet al., 2014) including in the seeds of Citrulluslanatusand subsequently drive to future discovery and development of plant-based drugs.

As being stated in the result, the preliminary phytochemical analysis conducted on ethanol extract of seeds of Citrulluslanatusrevealed the presence of phytoconstituents such as protein and amino acids, alkaloids, carbohydrates and glycosides, terpenoids, flavonoids as well as phenolic compound and tannins. Similarly, preliminary phytochemical analysis of Citrulluslanatus seeds that were extracted revealed the presence of flavonoids, saponins, tannins, alkaloids, glycosides, and proximate analysis indicated high concentrations of carbohydrate, protein, and fat, where all phytoconstituents except saponins, protein, and amino acids were found.in the ethanol extract of seeds of Citrulluslanatusin the present studyconducted.The result revealed that the ethanol extract of seeds of Citrulluslanatushas a positive analgesic and anti-pyretic activity effect due to the presence of a phenolic compound, tannins, alkaloids, glycosides and saponins

Fever, also known as pyrexia, is a common medical symptom characterised by a rise in body temperature above the normal range of 36.5$^0$C to 37.5$^0$C due to a rise in the body temperature regulation set-point(Anochieet al., 2013). Antipyretics are drugs that lower the body's temperature when it becomes too high(Bhattacharya et al., 2010).



Based on the results of ethanolic extracts of Citrulluslanatusseeds in yeast induced pyrexia in Wister albino rats are discussed below. The ethanolic extracts of Citrulluslanatusseeds at 400mg/kg showed a significant reduction in antipyretic activity compared to low dose, which is almost comparable to a standard drug. Paracetamol (150mg/kg) where it significantly lowered the temperature in yeast inducedpyrexia.

The extract which showed the highest anti-pyretic activity presented highly significant statistic values ($p<0.001$) for yeast induced pyrexia after the treatment. The present study establishes the anti-pyretic activity of extracts of Citrulluslanatusseeds. Negative group rats (treated with brewer’s yeast (15% w/v)) did not show any significant value for yeast induced pyrexia because it's used as a comparison group. The ethanol extract of Citrulluslanatusseeds at high dose (400 mg/ kg) and low

dose (200 mg/ kg) showed highly significant in rectal temperature. The ethanolic extract of Citrulluslanatusseeds in both low and high dose showed highly significant at the 4th hour which is almost comparable to a standarddrug.

Pain isboth a sensory and emotional experience and vital function of the human body, involving nociceptors and the central nervous system (CNS) to transmit messages from noxious stimuli to the brain. There are two types of COX enzymes that are COX-1 and COX-2. These enzymes produce prostaglandins that promote pain.The analgesic drugs work by blocking chemicals (prostaglandins) that sensitize the peripheral pain receptors to send a pain signal to the central nervous system(CNS). (Dr Danielle Reddi., 2008)

Thus, the extract which showed very good analgesic activity presented highly significant statistic values ($p<0.001$) for tail immersion test after the treatment. The present study establishes the analgesic activity of extracts of Citrulluslanatusseeds. The ethanol extract of Citrulluslanatusseeds at high dose (400 mg/ kg) showed high significant in the reaction of a tail flick, whereas the ethanol extract of Citrulluslanatusseeds at a low dose (200 mg/ kg) showed less significant analgesic activity.

The analgesic and anti-pyretic effect of Citrulluslanatusseeds can be attributed to one or more groups of the phytoconstituents observed in the extracts. Phytochemical screening of ethanolic extract of Citrulluslanatusseeds revealed the presence of flavonoids, saponins, tannins, glycosides, and alkaloids. Analgesic and anti-pyretic effects have been observed in flavonoids. The analgesic and anti-pyretic effect of the extracts in this study may, therefore, be due to the presence of flavonoids, tannins, alkaloid, saponins and phenolic compound. Flavonoids are widely shown to target prostaglandins which are involved in the pain perception through moderating opioidergic mechanism and pyrexia. These findings strongly recommend that ethanolic extract of Citrulluslanatusseeds have analgesic and anti-pyretic activity and their mechanisms of action may be mediated through inhibition of local peritoneal receptors which may be the involvement of cyclooxygenase inhibitionpotential.



**CONCLUSION**

The phytochemical screening of ethanolic extract of Citrulluslanatusseeds showed the presence of secondary metabolites such as tannins, phenol, volatile oil, alkaloids, carbohydrates, glycosides, oil and fats, terpenoids, and flavonoids. This study also highlights the significant anti-pyretic and analgesic activity of ethanolic extract of Citrulluslanatusseeds. The ethanolic extract of Citrulluslanatusseeds at a dose of 400mg/kg and low dose (200 mg/ kg) showed highly significant antipyretic activity. The ethanol extract of Citrulluslanatusseeds at high dose (400 mg/ kg) showed high significant in the reaction of a tail flick, whereas the ethanol extract of Citrulluslanatusseeds at a

low dose (200 mg/ kg) showed less significant analgesic activity. As a conclusion, this study produces information for the action of analgesic and anti-pyretic of Citrulluslanatusseeds which could give benefits to its ethanol medical utilization. However, further examination should be done to extract the active components that are important for these activities and to clarify the specific mechanisms of action.

**ACKNOWLEDGMENT**

Authors arethankful to KPJ Healthcare University College for providing necessary facilities to complete this study.

**CONFLICT OF INTEREST**

No conflict of interest

**REFERENCES**

Achyut Narayan Kesari, Prashant Rai, GeetaWatal, Santosh Kumar Singh. 2007. Assessment of glycemic potential of Musa paradisiaca stem juice. Retrieved from http://www.researchgate.net/publication/244790615_assessment of glycemic potential of Musa paradisiac stem juice.

Beldal, B., S C, M., &Londonkar, R. (2017). PRELIMINARY PHYTOCHEMICAL SCREENING, ANTIBACTERIAL ACTIVITY AND GC-MS ANALYSIS OF ASPARAGUS RACEMOSUS ROOT EXTRACT.International

Research Journal Of Pharmacy, 8(11), 91-94. doi: 10.7897/2230-8407.0811224

Chew. 2017. brewer's yeast induced fever method. brewer's yeast induced fever method Google Search. Retrieved from https://www.google.com.my/search?ei=vaLWynVNcX3vgTm372YCQ&q=brewer %27s+yeast+induced+fever+method&oq=brewer%27s+yeast+induced+fever+meth od&I=ps y-ab.3..33i160k1.2943.79126.0.79542.36.36.0.0.0.0.745.4345.18j10j1j6-2.31.0…0…11.64.psyab..5.31.4318…0j0i22i30k1j33i22i29i30k1j33i21k1.0.jE092j T20Is.

Critical Care. 2017. The pathophysiological basis and consequences of fever | Critical Care | Full Text. Retrieved from https://ccforum.biomedcentral.com/articles/10.1186/s13054-016-1375-5.

Chiu, Y., Huang, T., Chiu, C., Lu, T., Chen, Y., Peng, W., & Chen, C. (2012). Analgesic and Antiinflammatory Activities of the Aqueous ExtractfromPlectranthusamboinicus(Lour.) Spring. both in Vitro and in Vivo. Evidence- Based Complementary And Alternative Medicine, 2012, 1-11. doi: 10.1155/2012/508137

Europe PMC. 2017. Analgesic and Antipyretic Effects of SansevieriaTrifasciata Leaves - Europe PMC Article - Europe PMC. Retrieved from Available at: http://europepmc.org/articles/PMC2816473.

Helms, J., & Barone, C. (2018). Physiology and Treatment of Pain. Retrieved from http://ccn.aacnjournals.org/content/28/6/38.short

Jóźwiak-Bebenista, M., & Nowak, J. (2018). Paracetamol: mechanism of action, applications and safety concern. Retrieved from https://europepmc.org/abstract/med/24779190

Keller, A., Frey, M., Schmid, H., Steffen, R., Walker, T., &Schlagenhauf, P. (2008). Imported Typhoid Fever in Switzerland, 1993 to 2004. Journal Of Travel Medicine, 15(4), 248-251. doi:10.1111/j.1708-8305.2008.00216

Kim, H. (2014). Analysis of variance (ANOVA) comparing the means of more than two groups. Restorative Dentistry & Endodontics, 39(1), 74. doi: 10.5395/rde.2014.39.1.74

Ma, V., Chan, L., & Carruthers, K. (2014). Incidence, Prevalence, Costs, and Impact on Disability of Common Conditions Requiring Rehabilitation in the United States: Stroke, Spinal Cord Injury, Traumatic Brain Injury, Multiple Sclerosis, Osteoarthritis, Rheumatoid Arthritis, Limb Loss, and Back Pain. Archives Of Physical Medicine And Rehabilitation, 95(5), 986-995.e1. doi: 10.1016/j.apmr.2013.10.032

Max, M., Schafer, S., Culnane, M., Dubner, R., &Gracely, R. (1988). Association of pain relief with drug side effects in postherpetic neuralgia: A single-dose study of clonidine, codeine, ibuprofen, and placebo. Clinical Pharmacology And Therapeutics, 43(4), 363-371. doi:10.1038/clpt.1988.44

Motoc, D., Turtoi, N. C., Vasca, V., Vasca, E., Schneider, F., &Goldis, V. (2010). Physiology of Pain – General Mechanisms and Individual Differences. Journal Medical Aradean (Arad Medical Journal), XIII(4), 19–23. Retrieved from http://www.jmedar.ro/pdf/vol13/iss4/JMA13-4-10Motoc.pdf



News-Medical.net. 2017. Mechanism of Pain. Retrieved from https://www.news-medical.net/health/Mechanism-of-Pain.aspx.

PHYSIOLOGY OF PAIN. (2018). Retrieved from http://dspace.zsmu.edu.ua/bitstream/123456789/1988/1/15Physiology%20of%20Pain.pdf

Sadasivam, K., &Kumaresan, R. (2011). A comparative DFT study on the antioxidant activity of apigenin and scutellarein flavonoid compounds. Molecular Physics, 109(6), 839-852. doi: 10.1080/00268976.2011.556576

Saleem, T., &Basha, S. (2011). Analgesic, Antipyretic and Anti-inflammatory activity of dietary sesame oil in an experimental animal model. Retrieved from http://docsdrive.com/pdfs/pharmacologia/2011/172-177.pdf

Sasidharan, S., Chen, Y., Saravanan, D., Sundram, K., &Latha, L. (2010). Extraction, Isolation And Characterization Of Bioactive Compounds From Plants' Extracts. African Journal Of Traditional, Complementary And Alternative Medicines, 8(1). doi: 10.4314/ajtcam.v8i1.60483

Shakya, A. (2016). Medicinal plants: the Future source of new drugs. Retrieved fromhttp://www.florajournal.com/archives/2016/vol4issue4/PartA/4-2-13-120.pdf

Steeds, C. (2009). The anatomy and physiology of pain. Surgery (Oxford), 27(12), 507-511. doi: 10.1016/j.mpsur.2009.10.013

ScienceDirect. 2017. The anatomy and physiology of pain. The anatomy and physiology of pain - ScienceDirect. Retrieved from Available at: http://www.sciencedirect.com/science/article/pii/S0263931909002531.

Science Publishing Group. 2017. Watermelon Seeds as Food: Nutrient Composition, Phytochemicals and Antioxidant Activity: Watermelon Seeds as Food: Nutrient Composition, Phytochemicals and Antioxidant Activity: Science Publishing Group. Retrieved from Available at: http://article.sciencepublishinggroup.com/html/10.11648.j.ijnfs.20160502.18.html.

Tabiri, B. (2016). Watermelon Seeds as Food: Nutrient Composition, Phytochemicals and Antioxidant Activity. International Journal Of Nutrition And Food Sciences, 5(2), 139. doi: 10.11648/j.ijnfs.20160502.18

Wikipedia. 2017. Watermelon. Watermelon - Wikipedia. Retrieved from Available at: https://en.wikipedia.org/wiki/Watermelon.

Walter, E., Hanna-Jumma, S., Carraretto, M., &Forni, L. (2016). The pathophysiological basis and consequences of fever. Critical Care, 20(1). doi: 10.1186/s13054-016-1375-5

Young, G. B. (2014). Hyperthermia. In Encyclopedia of the Neurological Sciences (pp. 644–645).

Elsevier Inc. https://doi.org/10.1016/B978-0-12-385157-4.00331-6