Original Research

Antinociceptive, Antipyretic and Anti-inflammatory Activities of Natural Betaine

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ABSTRACT

Natural betaine is a natural amino acid derivative (trimethylglycine) that is found in beet molasses and their residues. Phytochemical, pharmacological, and toxicological properties of betaine have been tested in this study. Ninety mice were used to study betaine toxicity and analgesic activity. Fifty mice were distributed into five groups of ten mice to be used in the toxicological study while forty animals were distributed into four groups of ten mice each during the analgesic study. Forty-eight rats were used to investigate the anti-inflammatory and antipyretic activities of betaine. Rats were distributed into four groups of six animals each during both experiments. The anti-inflammatory (carrageenan-induced paw edema), antipyretic (Brewer's yeast-induced pyrexia), and analgesic (chemical and thermal-induced pain) actions of betaine have been studied. The results indicated that natural betaine has an oral LD50 of 5800mg\kg. Rats treated with betaine (100 or 200 mg/kg orally) exhibited a significant reduction in rats' paws thickness compared to the control group. The hyperthermia model and the analgesic model demonstrated good antipyretic and analgesic actions of betaine compared to the standard groups. These findings suggest that oral administration of natural betaine had significant anti-inflammatory and antipyretic activities in rats in addition to antinociceptive activity in mice.

Keywords: Natural betaine - Anti-inflammatory- Anti-nociceptive - Antipyretic-LD50.

INTRODUCTION

Pyrexia or fever is defined as a defense mechanism of the body against infectious or inflammatory factors and also can be developed in response to transplant rejection and damaged tissues. Pro-inflammatory cytokines such as tumor necrosis factor alpha TNF-α and interleukin 1β, α, β are initiated during inflammation, which in turn stimulates prostaglandin E2 synthesis and consequently raising the body temperature following the hypothalamus stimulation **(Chattopadhyay *et al*., 2005).** Consequently, there is an increase of vasodilation and blood vessels permeability following the release of phospholipase A2, cyclooxygenase- 2 (COX-2), 5-lipoxygenase (5-LOX), and inducible nitric oxide synthase (iNOS), which leads to enhance blood circulation, plasma fluids exudation, and leukocytes movement, mainly neutrophils to the damaged tissues **(Raju *et al*., 2014).** Inflammatory state and pyrexia help to establish a hostile environment for the infectious agents but when they exceed the required level, they result in unfavorable outcomes such as malignant hyperthermia or autoimmune diseases. Drugs with anti-inflammatory action also have antipyretic action for instance, e.g. nonsteroidal anti-inflammatory drugs (NSAIDs) **(Begum *et al*., 2011).** The therapeutic benefits of NSAIDs have been found as a result of COX-2 inhibition, while suppression of COX-1 induces digestive and urinary side effects. Gastrointestinal (GI) toxicity is by far the most common symptom of NSAIDs. Inhibition of COX-1 enzymes suppresses the synthesis of cytoprotective prostaglandins such as prostaglandin PGE2 and PGI2, which resulted in GI toxicity **(Suleyman *et al*., 2007).** Searching for safer natural therapeutic alternatives with potential antipyretic and anti-inflammatory activities such as betaine recently received attention as the present NSAIDs have been associated with various side effects on the body organs. Betaine is a fundamental constituent of the homocysteine-methionine cycle and is produced by the oxidation of choline. It was

detected for the first time in sugar beets (Beta vulgaris) and also has been identified in different plants, animals, and several microorganisms. Betaine has a critical role in cell signaling, cell membrane integrity besides the formation of neurotransmitters **(Kim *et al*., 2014).** Food consumption of choline and betaine has been recorded to have an anti-inflammatory impact. Interleukin 6 (IL- 6), TNF-α, COX-2, and iNOS expression significantly decrease in the tumors of mouse colon following dietary intake of betaine at doses of 1, 5, and 10 mg/kg for 16 weeks. Betaine has been known to have antioxidant activity, which increases the levels of superoxide dismutase (SOD) and glutathione peroxidase (GPx) against the production of reactive oxygen species (ROS) while decreasing malondialdehyde (MDA) levels **(Hassanpour *et al*., 2020).** Therefore, betaine therapy is beneficial against conditions associated with oxidative stress e.g., atherosclerosis, renal, and hepatic disorders **(Evran *et al*., 2018).** So, in this study, natural betaine has been investigated for its potential antipyretic, anti-inflammatory activity in a rat model as well as anti-nociceptive in a mice model.

MATERIALS AND METHODS

Natural Betaine: Natural betaine, 40 % solution was obtained as a patent preparation as oral water soluble solution produced by Agrana, AUSTRIA under trade name ActiBeet® .It was analyzed by Pharma Swede-Egypt and betaine HCL was considered as a reference.

Ethical approval: The experimental design of the present study was ethically approved by the Ethics Review Committee of the Faculty of Veterinary Medicine, Alexandria University, Egypt (Approval No. 0106321).

Animals:

1-Mice: Ninety mature male mice weighing 20-25 gm were used to study betaine toxicity and analgesic activity. The mice were obtained from the animal house, Faculty of Science, Alexandria University. Fifty mice were distributed into five groups of ten mice each to be used in the toxicological study while forty animals were distributed into four groups of ten mice each during the analgesic study of betaine.

2-Rats: Forty-eight mature male Wistar albino rats weighing 190-200 gm were used to investigate the anti-inflammatory and antipyretic activities of betaine. The rats were obtained from the animal house, Faculty of Science, Alexandria University. Rats were randomly distributed into four groups of six animals each during both experiments. Animals were kept at 23± 2°C in plastic cages with metal mesh leds and were exposed to 12 hr. dark/light cycle. All experimental animals (mice and rats) were acclimatized for two weeks before the starting of the experiment. During this period, the animals were kept in plastic cages with food and water ad libitum.

Determination of LD50: LD50 of betaine was performed on fifty mice (20-25 gm) using the method stated by Kerber (1941). Five groups of 10 mice each, one group used as a control, and the other four groups were treated with betaine on ascending doses (40, 80, 120,160, and 200mg/20g b.wt). Animals were observed for 48 hours to record toxic symptoms, rate of mortality, and postmortem changes within each group. LD50 of betaine was determined as the following formula:

$$LD_{50} = Dm - \frac{\Sigma(z \times d)}{n}$$

Where:

Dm = the highest dosage to kill the animals.

z = average number of dead animals between two successive groups.

d = the constant value between two successive doses.

n = number of animals per group.

∑ = the sum of (a × b).

B-Pharmacological studies:

1-Anti-inflammatory effect:

Male Wister rats of 150-200 gm b.wt were randomized into four groups of six animals. Group I was treated as control with induced inflammation only, group II and group III received orally 100 and 200 mg/kg of natural betaine, respectively, whereas group IV was treated as a standard by the administration of diclofenac sodium 30 mg/kg b.wt orally.

Preinjection volume of paws was measured immediately before carrageenan injection. 0.1 ml of 1% carrageenan solution dissolved in 0.9% saline was subcutaneously administered into the plantar surface of the left hind paw to induce edema or inflammation, thirty minutes before drug or betaine administration according to **Winter *et al*. (1962).** Vernier caliper was used to measure each rat paw thickness in mm to assess the inflammatory response caused by carrageenan after 1, 3, and 6 hours. The point of measurement was premarked with a permanent pen to be used as a reference in the following measurements.

2- Antipyretic effect:

Male Wister rats of 150-200 gm b.wt were randomized into four groups of six animals. Rectal temperature for each rat was measured then all animals were injected subcutaneously into the dorsum region by 12.5% Brewer's yeast suspension in normal saline to induce hyperthermia. Rectal temperature was measured 17 hours later using a digital thermometer for all animals to act as a baseline of high body temperature, which was compared to the antipyretic effect of betaine (animals with increased rectal temperature about 0.3-0.5 ºC have been chosen).

Group I was treated as control with induced pyrexia only, group II and group III were administered orally 100 and 200 mg/kg of natural betaine, respectively. Group IV served as a standard by oral administration of paracetamol 50 mg/kg b.wt. Rectal temperature was measured at 1, 3, and 6 hours after administration of betaine or medication following the method described by **(Teotino *et al*., 1963).**

3-Analgesic effect:

Hot plate test:

In the first experiment, the hot plate test was used to estimate the anti-nociceptive activity of betaine in mice as stated by Janssen and Jageneau (1957) and adjusted by (Jacob and Bosovski, 1961). Forty male mice of 20-25 gm b.wt were distributed into four groups of ten mice each. Group I served

as an untreated control group, while Group II and III were administered oral betaine at a concentration of 100 and 200 mg/kg b.wt, respectively, whereas group IV was administered oral paracetamol at a dosage of 50 mg/kg.

This method depends on a thermostatically controlled water bath with a temperature of 56 ± 0.5°C and a 2-liter beaker placed in a water bath to prepare the hot plate. Thirty minutes after the treatment has been orally administered, each animal was inserted into the beaker until the animal licked its paw or jumped. The reaction time of analgesic activity is calculated by the time passed until the mouse licked its paw or jumped. The reaction time in all groups was estimated at 1, 3, and 6 hours post oral administration of betaine in comparison to the control non-treated group and the standard group.

Writhing test:

In the second experiment, abdominal constrictions induced by acetic acid (writhing activity) were determined in mice as described by **Collier *et al*. (1968).** Writhing is defined as an exaggerated extension of the abdomen in conjunction with hind limbs extension induced by acetic acid **(Hassanpour *et al*., 2020)**. Forty male mice of 20-25 gm b.wt were distributed into four groups of ten mice each. Group I was treated as the untreated control group, while group II and III were administered oral betaine at doses of 100 and 200 mg/kg b.wt, respectively, while group IV was administered paracetamol orally at 50 mg/kg. Within 30 minutes, animals received 0.7% of the aqueous acetic acid solution by intraperitoneal injection (10 ml\kg b.wt), and then the mice were housed in transparent cages to be observed. Writhes number in each treated group was recorded for 20 minutes after the injection of the glacial acetic acid solution and compared to the writhes number of the non-treated control group. The number of abdominal stretching (writhes) was counted and the percentage of protection was determined as follows:

$$\text{Percentage of protection} = \frac{\text{Control mean} - \text{treated mean}}{\text{Control mean}} \times 100$$

C- Statistical analysis:

The results were expressed as mean ± SE of studied groups using the analysis of variance test (one way ANOVA) followed by Bonferroni test. All analysis was performed by statistical package for the social science software (SPSS Inc., Chicago, IL). Values of P<0.05 were considered significant.

RESULTS

A- Toxicological studies: LD50:

The obtained result revealed that oral administration of natural betaine at a dose up to 2000 mg/kg b.wt did not induce any mortalities or signs of toxicity. Soft stool was found in groups receiving various betaine doses. Signs of acute toxicity e.g., diarrhea, hematuria, lethargy, uncoordinated muscular movements, respiratory failure, and mortalities occurred following betaine administration at doses from 4000 up to 10000 mg/kg. After calculation, LD50 of natural betaine given orally was estimated to be 5800 mg/kg.

B- Pharmacological studies:

1- Anti-inflammatory activity:

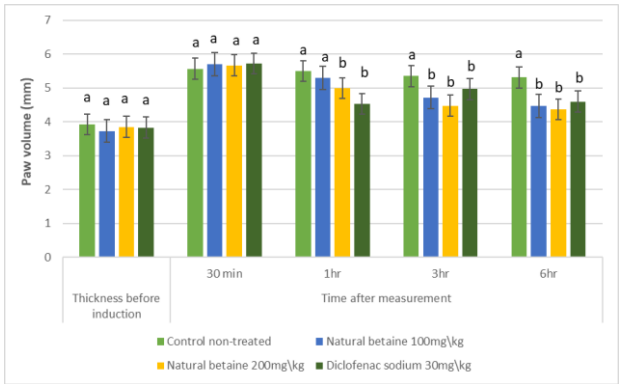
The natural betaine was tested for its anti-inflammatory effect by induction of rat paw edema using carrageenan suspension and the results were compared with the control data in Table (1) and graph (1). Injection of Carrageenan subcutaneously into the plantar area in rats paw in all animals produced a rapid substantial increase in the thickness of each paw. After 1, 3, and 6 hours, rats' paw thickness was significantly ($P \leq 0.05$) affected after treatment with natural betaine (200 mg/kg, orally) and diclofenac sodium (30mg/kg) when compared with the control group. Meanwhile, the group that received 100 mg/Kg natural betaine was significantly ($P \leq 0.05$) affected after 3 and 6 hr. only when compared with the control group. Six hours after carrageenan injections, the doses of betaine 100 mg/kg and 200 mg/kg reduced paw edema to (4.47±0.26) and (4.37±0.21), respectively, compared to the non-treated group (5.31 ±0.11). At this time, diclofenac sodium also reduced the paw to 4.6±0.24.

Table (1): The effect of natural betaine on Carrageenan induced edema (n=6).

Groups	Dose (mg/kg b.wt)	Thickness before induction	1hr	3hr	6hr
Control non treated	___	3.92 ±0.068 [a]	5.5 ±0.19 [a]	5.35 ±0.15 [a]	5.31 ±0.11 [a]
Natural Betaine	100	3.73 ±0.13 [a]	5.3 ±0.18 [a]	4.72 ±0.13 [b]	4.47 ±0.26 [b]
	200	3.85 ±0.095 [a]	5.0 ±0.19 [b]	4.48 ±0.17 [b]	4.37 ±0.21 [b]
Standard (diclofenac sodium)	30	3.83 ±0.094 [a]	4.53 ±0.52 [b]	4.97 ±0.12 [b]	4.6 ±0.24 [b]

Means with different letters (a, b) in the same column are significantly different at *a P-value*≤ 0.05 (Bonferroni test).

Graph 1: Distribution of anti-inflammatory activity of betaine extract with rat paw edema induced by Carrageenan in comparison with the standard Diclofenac sodium.



2-Antipyretic Activity:

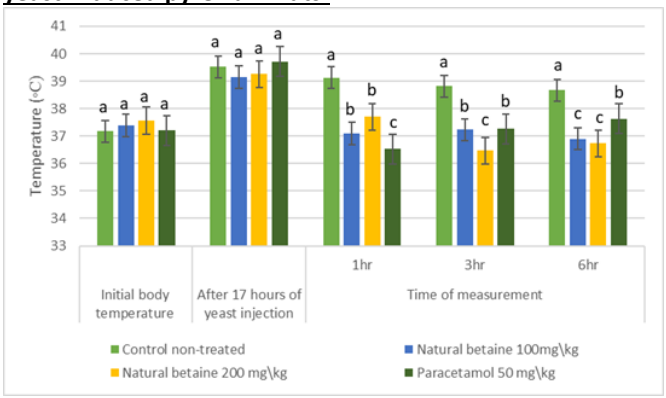
The natural betaine effect on rats' rectal temperature is shown in Table (2) and Graph (2). Rectal temperature of rats highly increased 17 hr. post subcutaneous injection of brewer's yeast suspension. Treatment with natural betaine in doses of 100 or 200 mg/kg resulted in a significant ($P \leq 0.05$) reduction in rectal body temperature of rats. At doses of (100, 200 mg/kg) betaine caused a dose-dependent antipyretic effect, generating marked antipyretic activity in hyperthermic rats induced by brewer's yeast.

Table (2): The Effect of natural betaine on Brewer yeast induced pyrexia on rats (n=6):

Groups	Dose (mg/kg) b.wt	Initial body temperature	After 17 hours of yeast	Time Of measurement		
				1hr	3hr	6hr
Control Non treated	____	37.18 ± 0.88^{a}	39.52± 0.33^{a}	39.13± 0.53^{a}	38.82± 0.81^{a}	38.67± 0.59^{a}
Natural Betaine	100	37.38 ± 1.42^{a}	39.14± 0.65^{a}	37.1± 0.37^{b}	37.23± 0.23^{b}	36.9± 0.41^{c}
	200	37.56 ± 0.68^{a}	39.26± 0.61^{a}	37.7± 0.33^{b}	36.47± 0.094^{c}	36.73± 0.12^{c}
Standard (paracetamol)	50	37.20 ± 0.93 ^{a}	39.72± 0.58^{a}	36.53± 0.18 ^{c}	37.27± 0.35 ^{b}	37.63± 0.15^{b}

Means with different letters (a, b, c) in the same column are significantly different at a *P-value* ≤ 0.05.

Graph 2. Effect of different concentrations of betaine on yeast-induced pyrexia in rats:



3-Analgesic effect:

Hot plate method:

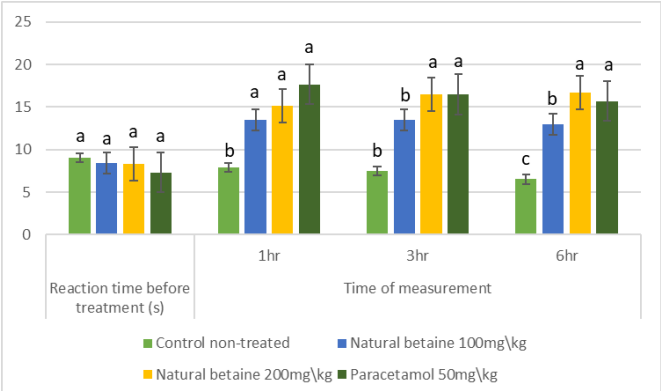
The effect of natural betaine on the hot plate test is presented in Table (3) and graph (3). Natural betaine was administered orally at various dosage levels and caused significantly prolonged reaction time in the hot plate test. Dosages of natural betaine (100 and 200 mg/kg) produced its analgesic activity in 30 minutes post-administration until the study ended. The highest reaction time 16.67±1.86 was noticed at a dosage of 200 mg/kg, at 6 hours after treatment with betaine compared to 6.00 ± 1.26 of the control non-treated group.

Table (3): The effect of natural betaine extract on the hot plate reaction time in mice (n=10):

Groups	Dose(mg/kg b.wt	Before treatment	Time of measurement		
			1hr	3hr	6hr
Control Non treated	____	9.05 ±1.23a	7.9 ±.83b	7.5 ± 0.74 b	6.51 ± 0.63c
Natural Betaine	100	8.4 ± 0.54a	13.50± 1.51a	13.50 ±1.87b	13.00±3.35b
	200	8.33 ±0.45a	15.17± 1.49a	16.50 ±1.88a	16.67±1.86a
Standard (paracetamol)	50	7.33 ±0.63a	17.67± 1.75a	16.50 ±1.87a	15.71±1.67a

Means with different letters (a, b, c) in the same column are significantly different at a *P-value* ≤ 0.05.

Graph 3. Effect of betaine on reaction time in the hot-plate test in mice



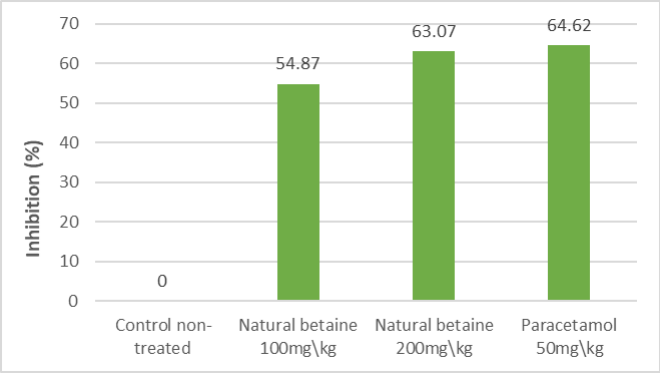
Writhing method:

Writhing test, which was induced by acetic acid was used to study the anti-nociceptive action of natural betaine as shown in Table (4) and graph (4). Natural betaine was found to have dose-dependent analgesic activity. Oral dosage of betaine (200 mg\kg) decreased writhes number with an inhibition percentage of 63.07 compared to the standard group treated with paracetamol (50 mg/kg) with an inhibition percentage of 64.67 %. Doses of 100 and 200 mg/kg of oral betaine extract significantly ($P \leq 0.05$) decreased acetic acid-induced abdominal contractions to 12.5±0.79 and 10.23±0.41, respectively, compared to the control group (27.7±1.64).

Table (4): The effect of natural betaine on an acetic acid-induced writhing in mice (n=10):

Groups	Dose in mg/kg body weight	No. of writhes/20 minutes	Inhibition (%)
Control non treated	___	27.7±1.64	0
Natural Betaine	100	12.5±0.79	54.87
	200	10.23±0.41	63.07
Standard Paracetamol	50	9.8±0.57	64.62

Graph (4): Percent of inhibition of pain response in writhing test induced by acetic acid in mice (n=10):



DISCUSSION

This study investigated the potential antipyretic, anti-inflammatory, and analgesic activities of natural betaine. Apparently, betaine demonstrated no mortalities at the maximum oral dose of 2000 mg/kg b.wt whereas the oral LD50 of natural betaine in mice was more than 5000 mg/kg b.wt. This means that, natural betaine is very safe and nontoxic compound indicated by a large value of LD50. In this respect, **Buck *et al.*, (1976)** reported that substances with LD50 lower than 10 mg\kg b.wt are considered extremely toxic while others with LD50 higher than 50 mg\kg are considered non-toxic.

The present study was also designed to assess the anti-inflammatory action of betaine using the Carrageenan-induced edema in rats paw. Edema induction in the paw of rats by various agents such as carrageenan suspension is a two-phase reaction in which the primary stage is initiated by histamine, serotonin, and kinins, while the secondary stage is induced by prostaglandins (arachidonic acid metabolism product by cyclo-oxygenase enzyme) and reactive oxygen species (ROS) formation **(Chen, 1993 and Panthong, 2004).**

At both 100 and 200 mg/kg, natural betaine exhibited a significant decrease in paw edema in rats after 1, 3, and 6 hours when compared to the standard group of diclofenac sodium. This result was found to be compatible with **(Adhikari *et al.*, 2017)** who found that beet roots extract at 100mg\kg, 200 mg\kg, and 400 mg\kg inhibited raw paw edema induced by Carrageenan by 25.83% , 33.75% and 50% ,respectively after four hours of treatment.

Reduction of paw edema at 1 and 6 hours by natural betaine is suggested to be contributed to its antagonistic effect on primary-stage compounds (histamine, serotonin, and kinins) or its antagonism on secondary-stage compounds (prostaglandins) or its formation by suppression of the COX enzyme followed by a consequent decrease in prostaglandins synthesis and may be contributed to the suppression of reactive oxygen species production by phagocytes (secondary phase mediator) inducing tissue damage after reaching the inflammatory site **(Cross *et al.*, 1987; Winrow *et al.*, 1993; Parke and Sapota, 1996).**

It is also suggested that betaine has a protective effect during cellular stress and also takes part in different biological processes. *In vitro*, studies have indicated that betaine has a significant anti-inflammatory effect. Betaine prevents the release of nitric oxide from activated microglia. *In vivo* , previous studies showed that betaine therapy in aged kidneys was found to suppress the activity of NF-$_{k}$B and other related genes expression as VCAM-1 (vascular cell adhesion molecule-1), TNF-α, and ICAM-1 (intracellular cell adhesion molecule-1), iNOS (inducible nitric oxide synthase) and COX-2 (cyclooxygenase-2) **(Go *et al.*, 2005; and Adhikari *et al.*, 2017).**

Several genes are involved in the pathogenesis of inflammation are controlled by the NF- B (transcription factor nuclear factor- $_{\kappa}$B) signaling pathway. The genes involved in the inflammatory process include the TNF-α (tumor necrosis factor-alpha), pro-inflammatory cytokines, IL-23 (interleukin 23), and IL-1β (interleukin 1 beta). NF-$_{\kappa}$ B is activated chronically in several diseases of inflammatory origin **(Monaco *et al.*, 2004; Aravilli *et al.*, 2017**). So, the nuclear factor-κB pathway has known to be a very important candidate for the treatment of inflammation. Betaine has been reported by several researchers to suppress the activity of NF-$_{k}$B and different genes involved in the inflammatory process **(Go *et al.*, 2005; Lee *et al.*, 2013)**.

Regarding the antipyretic activity of natural betaine, the current result indicates that betaine at both 100 and 200 mg/kg doses has significant antipyretic activity on high body temperature induced by Brewer's yeast in rats in comparison with the effect of paracetamol . **XU *et al.* (1986)** also stated that oral administration of betaine was found to have an antipyretic activity in vaccinated hyperthermic rabbits and had no effect on the temperature of normal healthy animals.

Spacer and Breder (1994) stated that pyrexia is induced by the release of pro-inflammatory cytokines as interleukin α, β, and TNF-alpha followed by an increase of PGE2 formation near the preoptic-anterior hypothalamus, which subsequently elevates body temperature**.** In addition, plants exhibiting antipyretic activity have been recorded to also have analgesic effects (**Dewan *et al.*, 2000).** The antipyretic activity of betaine is suggested to be attributable to the counteracting of prostaglandins on the anterior hypothalamus.

Concerning the analgesic activity of natural betaine, this study showed that natural betaine has both central and peripheral analgesic efficacy at both doses 100-200mg/kg. Formalin\acetic acid-induced writhing tests are the animal model of pain studies designed to assess the anti-nociceptive activities of various substances. Intraperitoneal injection of acetic acid stimulates the formation of pro-inflammatory cytokines and triggers the peripheral pain receptors on sensory nerve fibers which causes pain and hyperalgesia **(Hassanpour *et al*., 2020).** In the writhing test, the obtained results showed that doses of 100 and 200 mg/kg of oral betaine significantly ($P \leq 0.05$) inhibited acetic acid-induced abdominal contractions by 54.87% and 63.07%, respectively when compared to the standard group (64.62%).This result was supported by the findings observed by **Hassanpour *et al*.(2020)** who found that betaine administration significantly reduced the writhing test pain response by 59.37% when compared to the control group.

Since the effect of natural betaine was found to be 63.07% compared to standard paracetamol 64.67 %, it is suggested that natural betaine acts by a similar mechanism to NSAIDs through inhibition of cyclooxygenase or lipoxygenase pathway which block substance P function that stimulates pain in nerve endings. **Eun *et al*.,(2007)** stated that cellular treatment of betaine inhibited activation of NF-kB which controls the action of numerous genes, such as TNF, cyclooxygenase-2 (COX- 2), inducible NO synthase, subsequently followed by suppressed expression of cox-2 and TNF.

The central effect of betaine was identified using the hot plate test, by calculating the reaction time until the mouse jumped or licked its paws. It appears that betaine has a dose-dependent mechanism of action. The anti-inflammatory and anti-nociceptive effect of natural betaine may be associated with its bioactive constituents as alkaloids. In this respect **Blunden *et al*., (1981)** reported that betaines are known as QACs, which are quaternary ammonium substances with a completely methylated nitrogen atom that has a permanent positive charge. Betaine glycine is one of the best-known betaines and has a widespread distribution in plants. Early analysis of betaines relied generally on ion-exchange chromatography, paper chromatography, or TLC, with visualization of the separated compounds using Dragendorff's reagent **(Grieve and Grattan, 1983).**

CONCLUSION

From previous findings, it was concluded that natural betaine has anti-inflammatory, analgesic, and antipyretic activities. This provides a different approach to the treatment of pyrexia, inflammation, and pain. These activities confirm the value of betaine in folk medicine for treating serious inflammatory diseases. The study also suggests additional research for the isolation of phytochemicals related to each action.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this report.

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