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EVALUATION OF POLYHERBAL FORMULATION FOR ANTIPYRETIC ACTIVITY ON SMALL ANIMAL MODEL

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Keywords:

Fever, Antipyretic, Brewer's yeast, Hypothalamus, Biochemicaltest, Hematologytest, Polyherbal formulation (PHFs) extract

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ABSTRACT: Background: Fever is a part of a complex biological response due to pathogens, bacterial infection, damaged cells, drugs, toxins, *etc*. Fever is currently treated by NSAIDs. Unfortunately, NSAIDs damage the liver and kidney, inhibit COX-1, which affects the digestive system, and increase the risk of a blood clot. Therefore, the developments of potent antipyretic drugs from medicinal herbal plants are now under consideration. Polyherbal formulations (PHFs) was become resurgent due to the demand and consumption of herbal drugs. The present research aims to evaluate the antipyretic screening activity of PHFs in albino Wistar rats. **Material methods:** Different PHFs combinations were formulated using hydro-alcoholic extracts and explored the antipyretic activity of PHFs in albino Wistar rats. Male albino Wistar rats weighing 100-150g were selected and grouped among normal control, standard (Paracetamol; 150mg/kg) and treatment groups (PHF; 100 mg/kg, PHF; 300 mg/kg and PHF; 600 mg/kg) respectively. To check the safety parameters of PHFs extract, Hematological and biochemical tests were also performed. **Results:** PHFs (100mg/kg, 300mg/kg and 600mg/kg) shows antipyretic effect against brewer's yeast induced pyrexia in rats. It is noted that the % inhibition is 57.59 % in standard PCM, 43.39%in 100mg/kg, 42.68% in 300mg/kg and 42.66% in 600mg/kg dose. **Discussion and Conclusions:** The extract of PHFs has shown good antipyretic activity in Wistar rats. The present investigation comprised of pharmacological screening of PHFs extract in lab animals. The chemical constituents of PHFs extract were identified by different qualitative chemical test, and PHFs was selected for the pharmacological screening of antipyretic activity. The PHFs (100mg/kg, 300mg/kg, and 600mg/kg) show a significantly decreased pyretic effect against brewer's yeast-induced pyrexia in rats compared to the normal group. This suggests its efficacy in preventing hyperthermia. The extract of PHF_S shows important compounds such as carbohydrates, steroids, alkaloids, flavonoids, tannins, and triterpenes which may be responsible for antipyretic activity.

INTRODUCTION: Antipyretic refers to the substance which is used to reduce body temperature. In 1838 salicylic acid was first discovered from glucosidesalicin. In 1853 acetylsalicylic acid was synthesized, and this drug was commercially available in 1899.

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Acetaminophen for fever is a recently discovered drug which synthesized in 1950. Antipyretics commonly used are aspirin, acetaminophen, and other NSAIDs [1, 2].

Non-steroidal anti-inflammatory drugs are used in fever to diminish body temperature but do not cause hypothermia. Infectious fever is produced through the pyrogens, which include interleukins like IL-a, ß, and TNF-a, to increase PGE2 synthesis. Prostaglandin E2 (PGE2) is release from the arachidonic acid pathway. The arachidonic acid pathway is mediated by enzymes cycloxygenase-2,

phospholipase A2 and prostaglandin E2 synthase. PGE2 is a mediator for febrile response. PGE2 acts on neurons in the preoptic area by prostaglandin E receptor 3 (EP3) expressing neurons in the preoptic dorsimedial hypothalamus (DMH) [3]. Fever signals are sent to the dorsimedial hypothalamus, which stimulates the sympathetic output system and causes a non-shivering thermo genesis effect for heat generation and skin vasoconstriction to decrease heat loss from the body surface [4]. Pyrogen triggers fever and releases PGE2, which acts on the hypothalamus and generates back a response to the rest of the body. Hypothalamus works like a thermostat to maintain body temperature, and fever generated from hyperthermia by the circumstances surrounding it [5, 6]. Microbial tissue invasion sparks an inflammatory response and activates local vascular endothelial cells and leukocytes [7].

The extravasation of white blood cells into inflamed areas depends on a multistep interaction with endothelial cells regulated by various cytokines, chemokines, and adhesion molecules. Activated leukocytes release the pyrogenic cytokines interleukin-1b (IL-1b), tumor necrosis factor (TNF), and interleukin-6 (IL-6) [8, 9, 10]. The stimulation of vascular endothelial cells causes the production of prostaglandin E2 (PGE2). The signal of Peripheral inflammation may also travel along neuronal connections to activate the central nervous system and production of PGE2 [11, 12].

The preoptic neurons of the anterior hypothalamus (POAH) having definite E- prostanoid receptors arrange the febrile responses after the PGE2 signal. PGE2 modifies the neurons' firing rate, the event's result, and raised thermoregulatory set point [13]. To enhance heat production and reduce heat dissipation, regulated evocation of behavioral and physiologic changes occurs, creating the body temperature to reach the febrile set point. Fever is augmented in the peripheral and systemic inflammatory response due to the expression of inflammatory cytokines and enhancing leukocyte function [14, 15].

MATERIAL AND METHODS:

Test Animals: Male albino Wistar rats weighing between 100-150g were used for the antiulcer activity. Animals were received from the animal house of Goel Institute of Pharmacy and Sciences, Lucknow, India. All experimental animals were followed according to the Committee for the Purpose of Control and Supervision of Experiments on Animals (2014/PO/Re/S/18/CPCSEA). The animals were kept under standard optimum conditions of humidity, temperature (25±5°C), and light. The animals were adapted to animal house conditions and nurtured with a standard pellet diet and water *ad libitum*.

Grouping of Animals: Male albino Wistar rats weighing 100-150g were selected and grouped among normal control, standard (Paracetamol; 150mg/kg) and treatment groups (PHF; 100 mg/kg, PHF; 300 mg/kg and PHF; 600 mg/kg) respectively.

Plant Collection and Identification: In this study, different parts of selected whole plants of BM, EO fruits and WS's root were taken. The selected parts of plants were collected in and around the Central Institute of Medicinal and Aromatic Plants CSIR - Central Institute of Medicinal & Aromatic Plants, Lucknow, Uttar Pradesh, India. These plants were authenticated at Goel Institute of Pharmacy and sciences Lucknow vide authentication number Tech./Herb/2021-22/02. The voucher specimens of plants are placed in the department of pharmacognosy at our institution. Different parts of selected plants were extracted by solvents using Soxhlet apparatus using solvents like ethanol. The extracts were evaporated to dryness at low temperature (<40°C) under reduced pressure in a rotary evaporator. All extracts' percentage yield were calculated and stored in air-tight desiccators for further analysis.

Plant Materials: The study encompassed the preparation of poly-herbal formulations of the extract(s) of the parts of selected plants by using continuous hot extraction methods. The whole plant of *Bacopa monereri* (BM), fruits of *Emblica officinalis* (EO), and root of *Withania somnifera* (WS) were taken, and the extracts were prepared using standard methods. The major chemical constituents of these plants included bacosides in *Bacopa monnieri*, withanolides in *Withania somnifera* and gallic acid, and tannic acid *in Embelica officinalis* fruits extract, respectively [16, 17, 18].

Processing, Extraction and Storage of Plant Materials: The requisite parts of plants were cleaned out using distilled water and subsequently dried at room temperature until they were free from moisture.

After drying, the selected plant parts (BM, WS, and EO) were extracted by solvents like n-hexane, chloroform, ethyl acetate, and ethanol using the Soxhlet apparatus.

The extracts were evaporated to dryness at low temperature (<40°C) under reduced pressure in a rotary evaporator.

The percentage yield of all extracts was calculated, and the extracts were stored hermetically.

Phytochemical Screening: The extracts were subjected to preliminary phytochemical screening to detect various phytoconstituents viz. alkaloids, glycosides, steroids, terpenoids, phenolic compounds, saponins, carbohydrates, flavonoids, tannins, proteins and amino acids [19, 20].

RESULT: The present study includes a pharmacological screening of PHFs hydro alcoholic extract for Antipyretic activity.

This result includes physiological, phytochemical, hematology, and biochemical tests.

Percentage Yield: One kg of PHFs is shade dry for 10 days, giving a yield of about 25.30gm; the water extraction of PHFs gives 15.81% yield.

The initial weight of raw material = 400 gm Final weight of extract after dried = 25.30gm. So, the final percentage yield of dried extract was 15.81%.

Ash Value and Swelling Factor of PHFs: Loss on drying of PHFS is 0.30 gm which is normal and acceptable value. Continue drying weighing at 1 hr intervals for 5 hours shows the normal range.

The proximate analysis showed satisfactory results concerning the Ash value and Swelling factor of PHFS. The Ash value is 0.0360, and the swelling factor is 11.21% **Table 6.**

TABLE 1: PHYSIOCHEMICAL TEST PARAMETERS OF PHFs

S. no.	Test Parameters	Result (Values)
1.	Loss on drying	9.13%
2.	Total Ash value	0.0360
3.	Acid insoluble Ash	0.0136
4.	Water soluble Ash	0.0254
5.	Swelling factor	11.21%
6.	Alcohol soluble extractive	6%
7.	Water soluble extractive	12.2%

Phytochemical Analysis: The phytochemical analysis result of PHFs extract is reported in **Table 7**.

PHFs aqueous extract shows the presence of steroids, tannins, triterpenes, alkaloids, flavonoids, saponin, and glycoside; total protein and phenols are absent in dried bark extract.

Antipyretic Activity: The antipyretic activity of PHFS extract is represented in **Table 8** and **Graph 1**. A temperature rise is observed after brewer's yeast injection in all group rats except the control group.

The antipyretic activity of PHFS is evaluated by its ability to reduce body temperature after Brewer's yeast injection. The experiment results and observations are presented in **Table 8** and **Graph 1**.

The mean rectal temperature of all 5 groups of rats is 37.4 ± 0.29 to 37.54 ± 0.24 before brewer's yeast injection.

Brewer's yeast-treated rats show a 1.39°C (mean) increase in rectal temperature and ranges between 38.9 ±0.09 to 39.18 ±0.12.

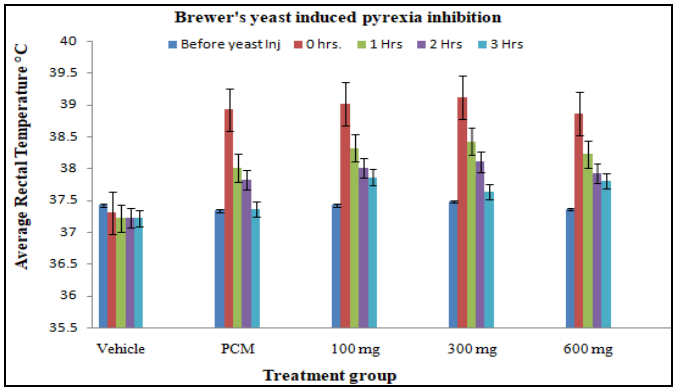
TABLE 2: INFLUENCE OF PHFs 100mg, 300mg, 600mg, AND PARACETAMOL (150mg/kg) ON BREWER'S YEAST INDUCED HYPERTHERMIA IN RATS COMPARE TO CONTROL

Group	Before yeast Inj	0hrs.	1 Hrs	2 Hrs	3 Hrs
Vehicle	37.42± 0.21	37.30± 0.07	37.22± 0.03	37.22± 0.03	37.22± 0.03
PCM	37.34± 0.27	38.92± 0.22	38.01± 0.35	37.82± 0.36	37.36± 0.29
PHFs 100MG	37.42±0.20	39.01± 0.08	38.32± 0.14	38.01± 0.21	37.86± 0.28
PHFs 300MG	37.48± 0.22	39.12± 0.10	38.42± 0.19	38.10± 0.17	37.63± 0.15
PHFs 600MG	37.36± 0.11	38.86± 0.07	38.22± 0.06	37.92± 0.02	37.80± 0.13

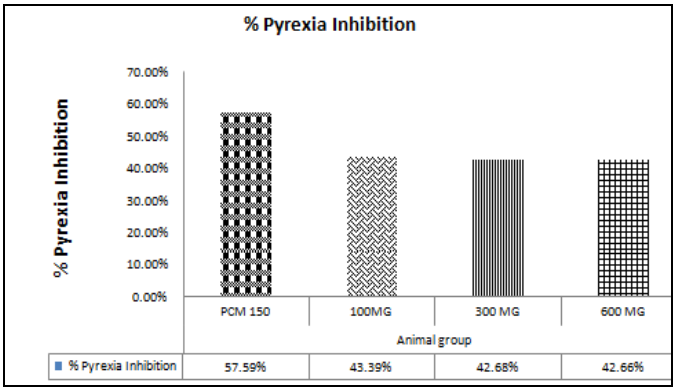
TABLE 3: CHEMICAL ANALYSIS OF PHFS EXTRACT, +: PRESENT, ++: SHOW MODERATE LEVEL, +++: PRESENT HIGHEST LEVEL, – ABSENT

S. no.	Constitute	Test method	Bark extract
1	Test for protein	Biuret test	+
2	Test for alkaloids	Dragandorff' sreagent test, Mayer's reagent test	++
3	Test for glycoside	Keller killani's test	+
4	Test for saponin	Foam test	+
5	Test for steroid	Salkowski test, Liebermanburchard test	++
6	Test for tannins	Ferric chloride test	+++
7	Test for phenols	Acetic acid test	–
8	Test for flavonoid	Shinoda test, Ferric chloride test	++
9	Test for trite pines	Salkowski test	+

Vehicle - Distilled water, PCM- Paracetamol, PHFS with three strength 100 mg, 300mg, 600 mg. Mean±SEM, No symbol: Non-significant compared to Control group.



GRAPH 1: GRAPH REPRESENTS TEMPERATURE LEVEL IN DIFFERENT GROUP



GRAPH 2: PERCENTAGE OF FEVER REDUCTION OF ANTIPYRETIC ACTIVITY

TABLE 4: EFFECTS OF PHFS ON HEMATOLOGICAL PARAMETERS

Groups	Hemoglobin (gram/dl)	RBC (Millions/mm^3)	Platelets	Pro-calcitonin
Vehicle	14.82± 1.09	7.260± 0.46	546±63.32	0.3748± 0.02
PCM	15.84± 0.72	7.614± 0.34	134.6± 48.14	0.0988± 0.02
PHFs 100mg	12.52± 3.12	6.058± 1.47	223.6± 110.54	0.1714± 0.081
PHFs 300mg	13.02± 1.28	6.232± 0.63	332.8± 51.47	0.2674± 0.02
PHFs 600mg	13.02± 2.84	6.648± 1.16	254.6± 81.85	0.1952± 0.04

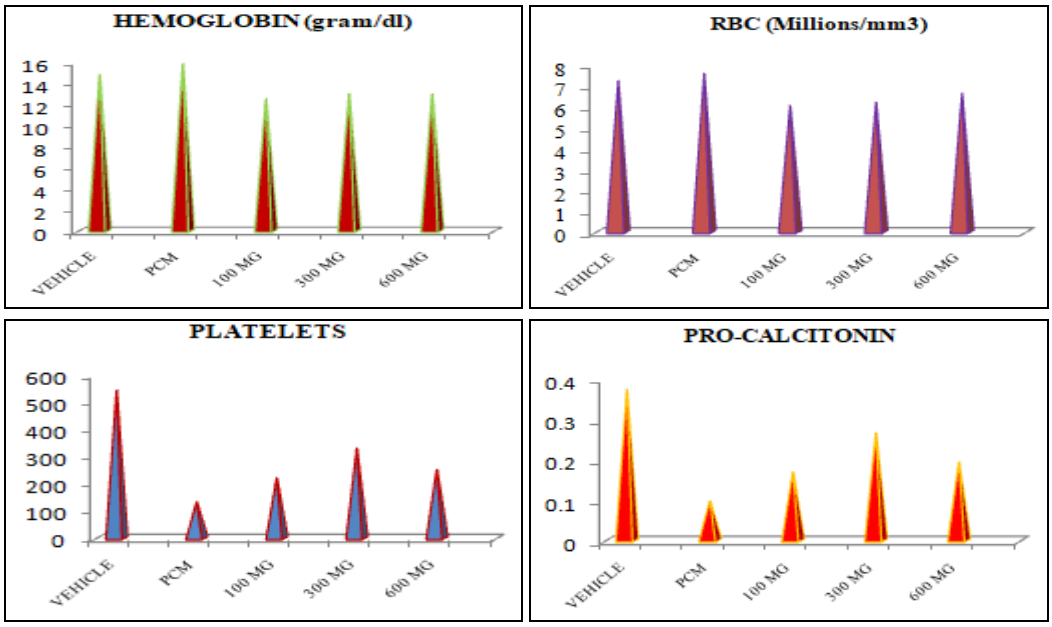


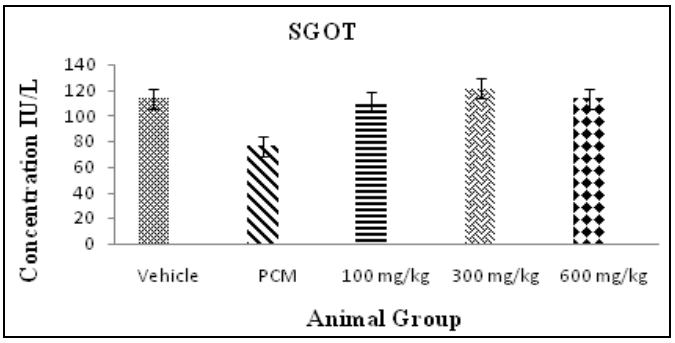
FIG. 1: EFFECT OF PHFS EXTRACT AS A SINGLE ACUTE ORAL DOSE ON RAT'S BODY WEIGHT, HEMOGLOBIN, RBC (REDBLOODCELLS), PLATELETS AND PRO-CALCITONIN PARAMETERS IN WISTER'S RAT

TABLE 5: PHFs BIOCHEMICAL TEST PARAMETERS

Test Name	Vehicle	PCM	PHFs 100mg	PHFs 300mg	PHFs 600mg
SGOT	113.32± 6.2	76.61± 10.32	110.65± 3.7	121.42± 10.5	113.48± 2.0
SGPT	13.96± 3.24	10.68± 2.34	14.17± 3.92	13.74± 1.68	11.65± 2.23
Cholesterol	113.31± 0.7	119.05± 3.8	125.21± 1.5	127.16± 7.2	125.71± 3.0
Creatinine	0.36± 0.0	0.33± 0.05	0.45± 0.02	0.33± 0.02	0.44±0.04
Bilirubin	3.62± 0.32	3.82± 0.38	3.92± 0.21	4.80± 0.42	5.23± 0.51

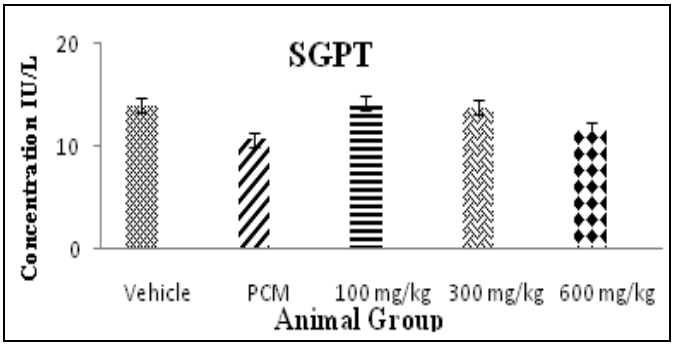
Biochemical Test Parameters:

SGOT: Slightly changes occur in aqueous extract PHFS 100mg, 300mg and 600mg (110.65± 3.7, 121.42± 10.5, 113.48 ± 2.0) treated rats as compare to vehicle group **Graph 2**. Standard paracetamol (76.61± 10.32) treated rats show decreased SGOT compared to the vehicle group (113.32± 6.2).



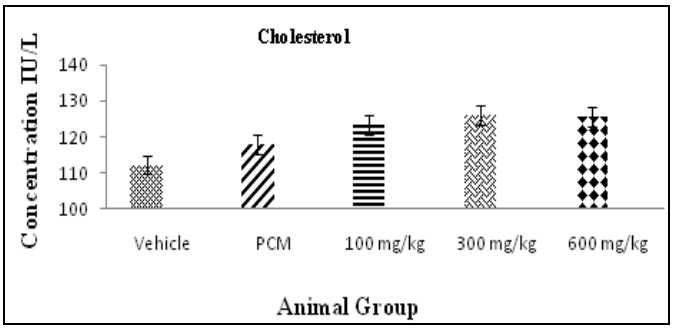
GRAPH 3: GRAPH REPRESENTS THE SGOT LEVEL. Columns are Mean ± SEM; Comparison is made on the basis of one way ANOVA followed by Bonferroni test. Treatment group are compared with vehicle (control) group(*p<0.05, **p<0.01,***p<0.001).

SGPT: Wistar rats, treated with aqueous extract of PHFS at the dose of 100mg/kg (14.17 ±3.92) is, show slightly increased SGPT levels compared to the vehicle group, while 300mg/kg(13.74± 1.68) shows approximately the same levels as compared to the vehicle group (13.96 ± 3.24). The standard paracetamol (10.68± 2.34) level is decreased as compared to the vehicle group (13.96±3.24).



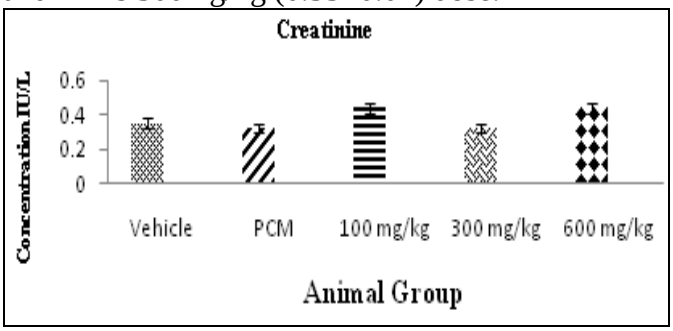
GRAPH 4: GRAPHRE PRESENTS SGPT LEVEL. Columns are Mean ±SEM; Comparison is made on the basis of one-way ANOVA followed by Bonferroni test. The treatment group is compared with the vehicle (control) group (p>0.05, so all groups are non-significant).

Cholesterol: Animals treated with PHFS aqueous extract at dose of 100mg/kg (125.21± 1.5), 300mg/kg (127.16± 7.2) and 600mg/kg (125.71± 3.0) shows increase cholesterol levels compare to vehicle group (113.31± 0.7). Paracetamol at 150mg/kg dose (119.05± 3.8) shows a slight increase level compared to the vehicle group (113.31± 0.7).



GRAPH 5: GRAPH REPRESENTS CHOLESTEROL LEVEL. Columns are Mean ±SEM; Comparison is made on the basis of one-way ANOVA followed by Bonferroni test. Treatment group are compared with vehicle (control) group (*p<0.05, **p<0.01, ***p<0.001, Non Significant)

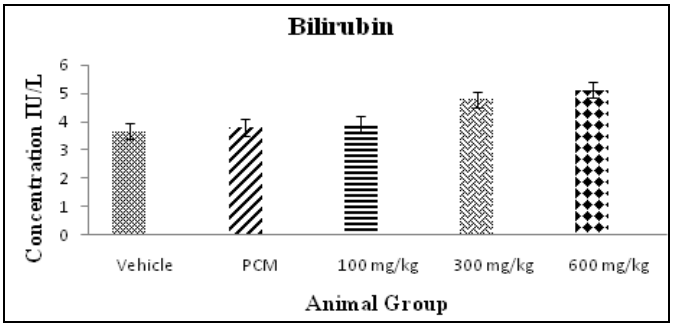
Creatinine: High creatinine level found in PHFS 100mg/kg (0.45 ± 0.02) and 600mg/kg (0.44 ±0.04) compare to vehicle group (0.36 ± 0.0), decrease level present in paracetamol 150mg/kg (0.33± 0.05) and PHFs 300mg/kg (0.33±0.02) dose.



GRAPH 6: GRAPH REPRESENTS CREATININE LEVEL. Columns are Mean ±SEM; Comparison is made by one way ANOVA followed by Bonferroni test. Treatment group are compared with vehicle (control) group (*p<0.05, **p<0.01, ***p<0.001: Nonsignificant).

Bilirubin: Wistar rats, treated with aqueous extract of PHFS at the dose of 100mg/kg (3.92± 0.21) is shows slightly increased bilirubin levels compared

to the vehicle group while 300mg/kg (4.80± 0.42) and 600mg/kg (5.23± 0.51) dose shows increase level. The standard paracetamol (3.82± 0.38) level is slightly increased compared to the vehicle group (3.62± 0.32).



GRAPH 7: GRAPH REPRESENTS BILIRUBIN LEVEL. Columns are Mean ±SEM; Comparison is made by one way ANOVA followed by Bonferroni test. Treatment group are compared with vehicle (control) group (*p<0.05, **p<0.01, ***p<0.001).

DISCUSSION: Fever may occur due to the infection or one of the tissue damage graft injection, inflammation, or other diseased states. Formation of pro-inflammatory mediator like cytokines-interleukin α, IL-β, IL-1β and TNF-α increase the synthesis of PGE2 (prostaglandin E2) near the preoptic hypothalamus area. It triggers the hypothalamus to increase body temperature. To treat fever, paracetamol and non-steroidal anti-inflammatory drugs are prescribed [21, 22]. NSAIDs inhibit cyclooxygenase 2 (COX-2) to reduce body temperature by inhibiting prostaglandin E2 biosynthesis [23]. All the NSAIDs are toxic to the body and affect the liver cells, heart muscles, glomeruli, cortex of the brain due to inhibition of COX-2. Natural cyclooxygenase 2 inhibitors having low selectivity with few side effects [24, 25]. Recently, new drugs from plant origin or herbal formulations have potent antipyretic activity with no or lower side effects compared to existing antipyretic drugs. So, herbal formulations are more potent compared to others.

CONCLUSION: The present investigation comprised pharmacological screening of PHFs extract in lab animals. Extraction of PHFs coarse powder with water yielded about 15.81% (w/w). The chemical constituents of PHFs extract were identified by different qualitative chemical test, and PHFs was selected for the pharmacological screening of antipyretic activity. The extract of PHFs shows important compounds such as carbohydrates, steroids, alkaloids, flavonoids, tannins, and triterpenes. Antipyretic activity of PHFs (100mg/kg, 300mg/kg, and 600mg/kg) shows antipyretic effect against brewer's yeast-induced pyrexia in rats. The % inhibition is 57.59 % in standard PCM, 43.39% in 100mg/kg, 42.68% in 300mg/kg and 42.66% in 600mg/kg dose. The extract of PHFs has shown good anti-pyeretic activity in Wistar rats.

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CONFLICTS OF INTEREST: Nil

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