Antibacterial and Antipyretic potential of biosythesized Zinc oxide and Iron oxide Nanoparticles of Methnolic fraction of *Euphorbia dracunculoides* L.

Umbreen Khattak[*1], Samin Jan[1], Rehman Ullah[2], Adil Muhammad[3]

[1] Department of botany, Islamia College University Peshawar, Pakistan

[2] Department of Botany, University of Peshawar, Pakistan

[3] Infection Medicine, Deanery of Biomedical Sciences, Edinburgh medical School, The University of Edinburgh, United Kingdom

Abstract

This study aimed to explore the biological potential of the *Euphorbia dracunculoides* mediated zinc oxide and iron oxide nanoparticles against bacterial strains and pyrexia. The result indicated that the plant extract and both nanoparticles showed promising antibacterial activity in a dose-dependent manner against bacterial strains i-e *E. faecalis*, *E. coli*, *B. cereus*, *S. aureus*, and *P. aeruginosa*. In vivo, the Antipyretic activity of plant extract and iron oxide nanoparticles was effective significantly decreasing body temperature in a dose-dependent manner but zinc oxide showed a non-significant decrease in body temperature. The result summarized that both nanoparticles are safe for the preparation of drugs.

Introduction

The elevation of body temperature over the usual range is referred to as pyrexia (Rakib *et al*., 2020). Tumor malignancy, Inflammation, and other pathological conditions like graft rejection can all cause pyrexia. As a result of infection or tissue injury, fever develops (Asante *et al*., 2019). Antipyretic medicines derived from plants have been used to treat fever for a long time (Sultana *et al*., 2015). Antipyretics are medications that lower body temperature in conditions like fever, which is a natural aspect of the immune system's reaction to illness. If someone doesn't have a fever, they won't impact their regular body temperature. A rise in blood temperature causes heat loss, which leads to an increase in heat production. Antipyretics allow the hypothalamus to counteract a rise in temperature caused by interleukin. The body will then

strive to reduce the temperature, resulting in a decrease in fever (Sajeesh *et al*., 2011). Fever is linked to disease symptoms such as tiredness, difficulty focusing, lethargy, depression, and anorexia. Increased muscular tone causes shivering as the set point rises. Antipyretic medicine, on the other hand, is useful in decreasing temperature and improving the comfort of the affected individual (Khan *et al*., 2015). Toxicology is the study of the harmful effects of natural substances on living beings. It is used to determine whether a medicine is safe, capable, and effective by testing it on mice, rats, guinea pigs, and rabbits, among other animals (Barkatullah *et al*., 2015). Toxicological study of various extracts of medicinally important plants is employed for assessment of possible potential toxic effects to be used clinically or preclinically (Porwal *et al*., 2017). Plants have hundreds of hazardous phytoconstituents that can kill an organism even if just a little amount is consumed. Medicines that have not been subjected to an experiment or a toxicological screening should not be utilized in clinical settings (Uddin *et al*., 2012). Acute toxicological studies aid in determining whether or not a new medicine is clinically safe. Understanding the chemistry and metabolism of the herb's ingredients can help forecast toxicity concerns. Misidentification, differences in composition, and other factors contribute to issues such as overdosing or under dosing, as well as adulteration (Nelson *et al*., 2014). Toxicology is a branch of pharmacology concerned with the effects of biologically active compounds on living creatures. To prove the usefulness and protection of innovative treatment, acute toxicity is carried on rats, mice, and other animals (Baliga *et al*., 2004). In clinical trials, no pharmaceutical substances are used, without safety evaluation in the preclinical laboratory. Toxicological investigations aid in determining whether or not a new medicine should be used in clinical practice (Heinrich *et al*., 2012).

Because of their abundance of bioactive chemicals, such as flavonoids and phenolic compounds, medicinal plants have been utilized to treat a variety of ailments in people and animals. These compounds are characterized as secondary metabolites with potent biological activity like antioxidant, anti-inflammatory, antimicrobial, hypoglycemic, antihypertensive, and antiviral activities (Ghomari *et al*., 2019). Bacterial and fungal infections kill a lot of people every year. Antibiotics have therefore been revolutionized in the treatment of a wide range of bacterial and fungal illnesses. Because of the resistance of microorganisms to antibiotics, it is essential to evaluate natural plant assets for the isolation of antimicrobial substances (Seddik *et al*., 2010). Due to their antibacterial and antioxidant capabilities, several plant species have been employed

in the food sector (Mahdavi *et al*., 2019). Many Herbal extracts are proven to be the best antimicrobial agents against Gram-positive/negative bacteria, molds, and yeasts (Rezaei and Pirbalouti, 2019). Antibiotic overuse enhanced the resistance of several pathogenic microorganisms, lowering cure effectiveness and raising fatality rates (Aoki and Ueda, 2013). The use of natural medicines derived from plant extracts or their active components as antimicrobial agents has grown in popularity due to their renewable nature, fewer side effects, low cost, and greater accessibility (Nasr *et al*., 2019).

In the present study, zinc oxide and iron oxide nanoparticles synthesized from *Euphorbia dracunculoides* plant extract are analyzed for the first time to be antibacterial agents, toxicological agents, and antipyretic agents.

Materials and Method

2.1 Acute toxicity study

The standard approach of Baliga *et al*. (2004) was used to conduct an acute toxicological investigation on crude methanolic fraction, zinc oxide, and iron oxide nanoparticles of *Euphorbia dracunculoides*.

Procedure:

In the bioassay, BALB/c mice weighing 18-24 grams of either sex were employed.

Before the experiment began, the animals were housed in cages, accommodated in typical ambient conditions, and permitted to fast for 12 hours by removing food and drink.

Following that, the mice were divided into 13 groups, each with six replicates. Normal saline was given to Group 1, crude methanolic extract was given to Groups 2–5, and zinc oxide nanoparticles were given to Groups 6–9 at doses of 200 mg/kg, 400 mg/kg, 600 mg/kg, and 800 mg/kg body weight, respectively.

The same doses of Iron oxide nanoparticles were given to groups 10-13.

The animals were watched for many hours after administration for any behavioral changes or the manifestation of any toxicity symptoms.

2.2 Antibacterial assay

Test microorganism:

The antibacterial action was tested on *Escherichia coli*, *Staphylococcus aureus*, *Enterococcus feacalis*, *Bacillus cerus*, and *Pseudomonas auroginosa*, among other bacteria.

Preparation of Solution:

3mg extract, zinc oxide, and iron oxide nanoparticles were dissolved in 1 ml DMSO (dimethyl sulfoxide) to make the stock solution.

The reference standard (positive control) was amoxicillin, while the negative control was dimethylsulfoxide (DMSO).

Method

Using the agar well diffusion method, the antibacterial activity of E. dracunculoides was determined (Rout *et al*., 2012).

Under sterile conditions, 100 ul of diluted inoculums (106 CFU/ml) of test cultures were thoroughly mixed with 20 ml of molten sterile tryptic soya agar and poured into pre-sterilized Petri dishes. All plates were left at 4°C for 30-40 minutes to set. Six mm diameter holes were drilled in

the center of each seeded plate. After that, 0.1 ml of the test solution was aseptically filled into the holes (crude methanol and Zinc oxide and Iron Oxide nanoparticle). A standard disc of antibiotic amoxicillin (10 ug) was used as a positive antibacterial control. DMSO is used as a countermeasure. After that, all plates were incubated at 37 °C + 1 °C for 24 hours. Antibacterial activity was measured using the zone of inhibition around the well. The diameter of the inhibitory zone was measured in millimeters using a vernier caliper. All tests were run three times to reduce test errors.

2.3. Antipyretic activity

Using a modified version of the brewer yeast pyrexia induction model, the antipyretic potential of *Euphorbia dracunculoides* was investigated (Panthong *et al*., 2007, Smith and Hambourger, 1935, Bose *et al*., 2007).

Procedure:

The experimental BALB/c mice were randomly separated into 14 groups, each with six mice, to determine the antipyretic potential of plant test materials.

The initial rectal temperature of each mouse was verified with a digital thermometer after grouping (MedisignMANA & CO Pakistan).

Before inducing pyrexia, the data was recorded as the original temperature.

To induce pyrexia in mice, 20 ml/20% brewer's yeast (*Saccharomyces cerevisiae*) was injected subcutaneously and the mice fasted from food and drink for 24 hours. After 18 hours, the animals with a temperature increase of 0.3-1 0 C were chosen, and the temperature increase was observed again after induction of pyrexia.

The mice in groups 1 and 2 were given either normal saline (1cc) or paracetamol (10mg/kg) of body weight and were designated as negative and positive controls, respectively. Methanolic fraction extract was given orally to mice in groups 3, 4, and 5 at doses of 100mg/kg, 200mg/kg, and 300mg/kg body weight, respectively. Zinc oxide was given to groups 6, 7, and 8, while iron oxide nanoparticles were given to groups 9, 10, and

11 at doses of 100mg/kg, 200mg/kg, and 300mg/kg body, respectively. After administration of the plant test sample and the reference medication at intervals of 1-3 hours, the change in rectal temperature was measured again. After the third hour, the final data was recorded as mean and SEM, and the percentage change in temperature was calculated using the formula below.

percent change in paw volume (edema)= $\frac{Ap-At}{Ap}\times 100$

where, Control group Ap= Average inflammation of the hind paw (edema)

At= The test group's average inflammation of the hind paw (edema).

RESULTS

Antibacterial activity

Antibacterial efficacy of *Euphorbia dracunculoides* methanolic extract mediated iron oxide and zinc oxide nanoparticles were evaluated against bacterial strains i-e *B. cereus*, *S. aureus*, *E. coli*, *Enterococcus faecalis*, and *P. aeruginosa*. The antibacterial efficacy of plant extract and nanoparticles were calculated compared to streptomycin (positive control) and DMSO (negative control). The zone of inhibition in mm was calculated against various bacterial strains are shown in Table 1. At 50µg/ml, plant extract delimited the bacterial growth by 12.58%, 17.09%, 12.30%, 21.46%, 15.78% compared to streptomycin against *Bacillus cereus*, *Staphylococcus aureus*, *Enterococcus faecalis*, *E. coli* and, *Pseudomonas aeruginosa*,. Zinc oxide nanoparticles inhibited the growth of *Bacillus cereus*, *Staphylococcus aureus*, *Enterococcus faecalis*, *E. coli*, *Pseudomonas aeruginosa*, by 20.86%, 21.79%, 23.07%, 19.76% and 17.66% compared to the standard streptomycin at 50 µg/ml. while at 50 µg/ml iron oxide nanoparticles showed 26.49% inhibition against *Bacillus cereus*, 35.89% inhibition against *Staphylococcus aureus*, 30% inhibition against *Enterococcus faecalis*, 21.73% inhibition against *E. coli* and, 28.19% inhibition against *Pseudomonas aeruginosa*. At the concentration of 100 µg/ml, plant extract inhibits the growth of *B.cereus*, *S.aureus*, *E. faecalis*, *E.coli* and *P. aeruginosa* by 17.88%, 27.77%, 23.84%, 21.73% and 27.44% compared to the positive control streptomycin, respectively. Similarly, the antibacterial efficacy of plant-mediated

zinc oxide nanoparticles delimited the growth of bacteria by 34.76%, 49.14%, 51.15%, 45.05% and, 47.74% of *B. cereus*, *S. aureus*, *E. faecalis*, *E. coli* and *P. aeruginosa*, at 100 µg/ml dose while *E. dracunculoides* mediated iron oxide nanoparticles revealed 40.39% inhibition against *B. cereus*, 57.26% inhibition against S. *aureus*, 56.92% inhibition against *E. faecalis*, 49.01% inhibition against *E. coli* and 48.49% inhibition against *P. aeruginosa* at the concentration of 100 µg/ml.

Because of the above result it was concluded that the activity showed by plant extract, zinc oxide and iron oxide nanoparticles was dose-dependent. It was noted that by increasing the concentration of plant extract and nanoparticles, both gram-negative and gram-positive bacteria growth will be more effectively inhibited. However, plant-mediated Zinc oxide and Iron oxide nanoparticles were more effective than *E. dracunculoides* methanolic extract against both gram-positive and gram-negative bacterial strains.

The results shown in table 1 specify that the antibacterial efficacy of plant extract, ZnONPs, and iron oxide nanoparticles vary against various strains of bacteria. Plant extract and its nanoparticles showed a zone of inhibition + SEM which is shown in Table 1. Percent inhibition of gram positive bacteria and gram negative bacteria as shown in fig 1 and 2.

Table 1. Antibacterial activity of *E. dracunculoides* mediated Zinc oxide and Iron oxide nanoparticles

Zone of inhibition in mm+ inhibition (%)					
Treatments	*Bacillus cereus*	*Staphylococcus aureus*	*E. coli*	*Pseudomonas aeruginosa*	*Enterococcus. Faecalis*
DMSO	-	-	-	-	-
streptomycin	30.2±0.4 (100)	23.4±0.6 (100)	25.3±0.4 (100)	26.6±0.3 (100)	26±0.2 (100)
DMSO	-	-	-	-	-

Extract (50µg/ml)	3.8±0.1 (12.58)	4.0±0.2 (17.09)	5.43±0.29 (21.46)	4.2±0.4 (15.78)	3.2±0.4 (12.30)
Zinc oxide (50µg/ml)	6.3±0.7 (20.86)	5.1±0.3 (21.79)	5.0±0.3 (19.76)	4.7±0.4 (17.66)	6.0±0.2 (23.07)
Iron oxide (50µg/ml)	8.0±0.2 (26.49)	8.4±0.3 (35.89)	5.5±0.4 (21.73)	7.5±0.7 (28.19)	7.8±1.0 (30.0)
Extact (100µg/ml)	5.4±0.4 (17.88)	6.5±1.0 (27.77)	5.5±0.7 (21.73)	7.3±0.7 (27.44)	6.2±0.3 (23.84)
Zinc oxide (100µg/ml)	10.5±0.4 (34.76)	11.5±0.4 (49.14)	11.4±0.6 (45.05)	12.7±0.3 (47.74)	13.3±0.5 (51.15)
Iron oxide (100µg/ml)	12.2±0.4 (40.39)	13.4±0.4 (57.26)	12.4±0.6 (49.01)	12.9±0.3 (48.49)	14.8±0.5 (56.92)

Data represented as Mean ± SEM (3 replicates for each concentration)

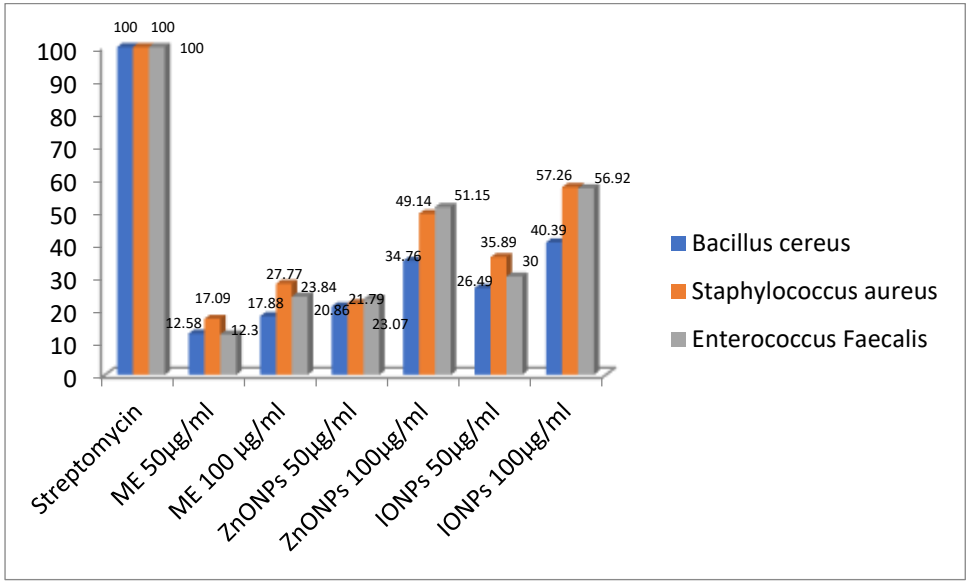

Fig.1. Percent inhibition of Gram-positive bacteria by methanolic fraction, zinc oxide and iron oxide nanoparticles

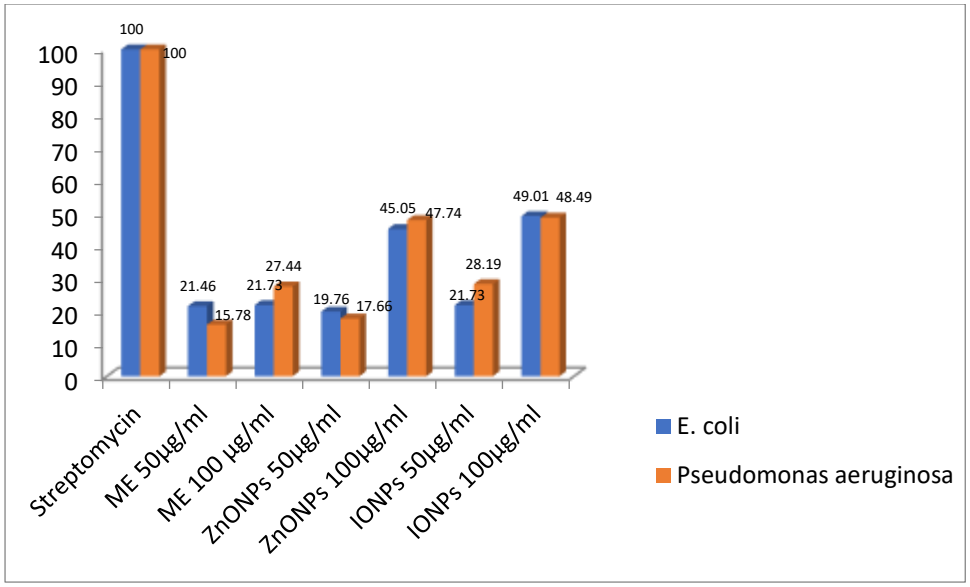

Fig.2. Percent inhibition of Gram-negative bacteria by methanolic fraction, zinc oxide and iron oxide nanoparticles

Acute toxicity

In the present study, in vivo toxicity assay of the methanolic fraction of *Euphorbia dracunculoides*, ED-mediated Iron, and zinc oxide nanoparticles were studied in mice. At the highest experimental dose, 1000mg/kg.bw plant extract did not show any physical symptoms in all tested mice while iron oxide and zinc oxide nanoparticles were observed at the dose of 600mg/kg.bw with no obvious symptoms in tested swiss albino mice. (Table, 2). This study disclosed the safety of plant extract and its nanoparticles for further study.

Table 2. Acute toxicity assay of *E.dracunculoides* methanolic fraction, ZnONPs and Iron oxide nanoparticles

Treatments	Doses (mg/Kg.bw)	Response
Saline	10ml/Kg.bw	(Alive) normal
Plant extract	200	(Alive) normal
	400	(Alive) normal
	600	(Alive) normal
	1000	(Alive) normal
Zinc oxide nanoparticles	200	Alive (normal)
	400	Alive (normal)
	600	Alive (normal)
	800	dead
Iron oxide nanoparticles	200	Alive (normal)
	400	Alive (normal)
	600	Alive (morbid)
	800	dead

Antipyretic activity

Antipyretic activity of *Euphorbia dracunculoides*, zinc oxide nanoparticles, and iron oxide nanoparticles was carried out using brewer yeast for inducing pyrexia in swiss albino mice (tested animals). Change in body temperature of tested animals and mean inhibition of pyrexia by plant extract and its nanoparticles has been observed for five hours which is shown in table 3 and fig 3.

Brewer yeast was injected subcutaneously into tested animals. After 18 hours of injection, only those mice were grouped whose body temperature elevated. The mice received paracetamol (10mg/kg) and plant extract test drugs (plant extract and nanoparticles). The mice treated with the positive control (paracetamol) 10mg/kg showed a decline after 1 hour in body temperature (from 38.86±0.25 to 37.47 ± 0.26). After the 3rd and 5th hours, a highly significant decrease occurred in the body temperature (36.64±0.16, 36.38±0.06) as compared to the negative control, and the behavior of mice was completely normal. At 100mg/kg, plant extract shows significant reduction ($p<0.05$) after 3rd hour of drug administration (37.78±0.20) which is turned highly significant ($p<0.01$) after 5th hour (37.15±0.12) post-dosing. Similarly, at 200mg/kg and 300mg/kg dose, it shows a significant decrease in body temperature after 3rd hour (37.66±0.42, 37.60 ± 0.31) while a highly significant ($p<0.01$) decrease occurs after 5th hour. ZnONPs show a nonsignificant decrease at (100mg/kg, 200mg/kg, and 300kg/kg) after 1st and 3rd hour of Zinc oxide administration but after 5th hour it showed a significant decrease ($p<0.05$). Iron oxide nanoparticles at the dose of 100mg/kg showed a significant ($p<0.05$) decrease after 3rd hour (37.44± 0.13) while a highly significant ($p<0.01$) decrease in body temperature occurs after 5th hour (37.13±0.15). At 200mg/kg, iron oxide nanoparticles cause a significant decline in rectal temperature after 1st and 3rd hours which is turned highly significant ($p<0.01$) after 5th hour. At the dose of 300mg/kg, iron nanoparticles show a significant effect after 1 hour of drug administration while a highly significant decrease occurs after 3rd and 5th hour as compared to negative control

The above result documented that plant extract and iron nanoparticles were effective in normalizing the body temperature while ZnONPs shows a non-significant decrease in body temperature. Plant extract and iron nanoparticles significantly decrease pyrexia in the following descending order Iron oxide > plant extract > Zinc oxide nanoparticles.

Table 3. Antipyretic activity of methanolic fraction of *E.dracunculoides*, Zinc oxide nanoparticles and Iron oxide nanoparticles

S No.	Treatment	Dose (mg/kg)	Normal body Temperature	Temperature after brewer yeast injection	Rectal Temperature ^{0}C (Mean ± SEM)		
					After 1 hour	After 3hours	After5 hours
1.	NS	1cc	36.47 ± 0.12	38.53 ± 0.09	38.97 ± 0.12	39.35 ± 0.20	39.61 ± 0.17
2.	Std	10mg/kg	36.57 ± 0.15	38.86±0.25	37.47 ± 0.26*	36.64±0.16**	36.38±0.06**
3.	EDM	100mg/kg	36.54±0.15	38.85±0.26	38.61±1.06	37.78±0.20*	37.15±0.12**
		200mg/kg	36.77±0.13	38.77±0.13	37.98±0.28	37.66±0.42**	37.22±0.26**
		300mg/kg	36.90±0.22	38.89±0.25	37.75±0.18	37.60 ± 0.31**	37.24±0.29**
4.	Iron oxide NPs	100mg/kg	37.16±0. 25	38.86±0.21	38.67± 0.45	38.51±0.17	38.01±0.43*
		200mg/kg	36.99±2.44	38.91±0.49	38.60±0.36	38.45± 0.30	38.12±0.26*
		300mg/kg	37.32±3.53	38.69±0.28	38.53±0.17	38.31±0.51	38.26±0.34
5.	Zinc oxide NPs	100mg/kg	37.01± 0.34	38.49±0.37	37.58±0.18	37.44± 0.13**	37.13±0.15**
		200mg/kg	37.31±0.15	38.81±0.17	37.47±0.19*	37.28±0.19**	37.05±0.17**
		300mg/kg	37.02±0.18	38.61±0.16	37.31±0.15**	37.25±0.26**	37.02±0.18**

The data for antipyretic activity (change in body temperature) was described as Mean ± SEM of six replicates of mice for each group. Subjected to Oneway ANOVA following Dunnett's post-hoc, *P<0.05 presented statistically significant and **P<0.01 showed highly significant results.

Key Words: NS: Normal saline, Std: Standard Paracetamol, EDM: *Euphorbia dracunculoides* methanolic fraction

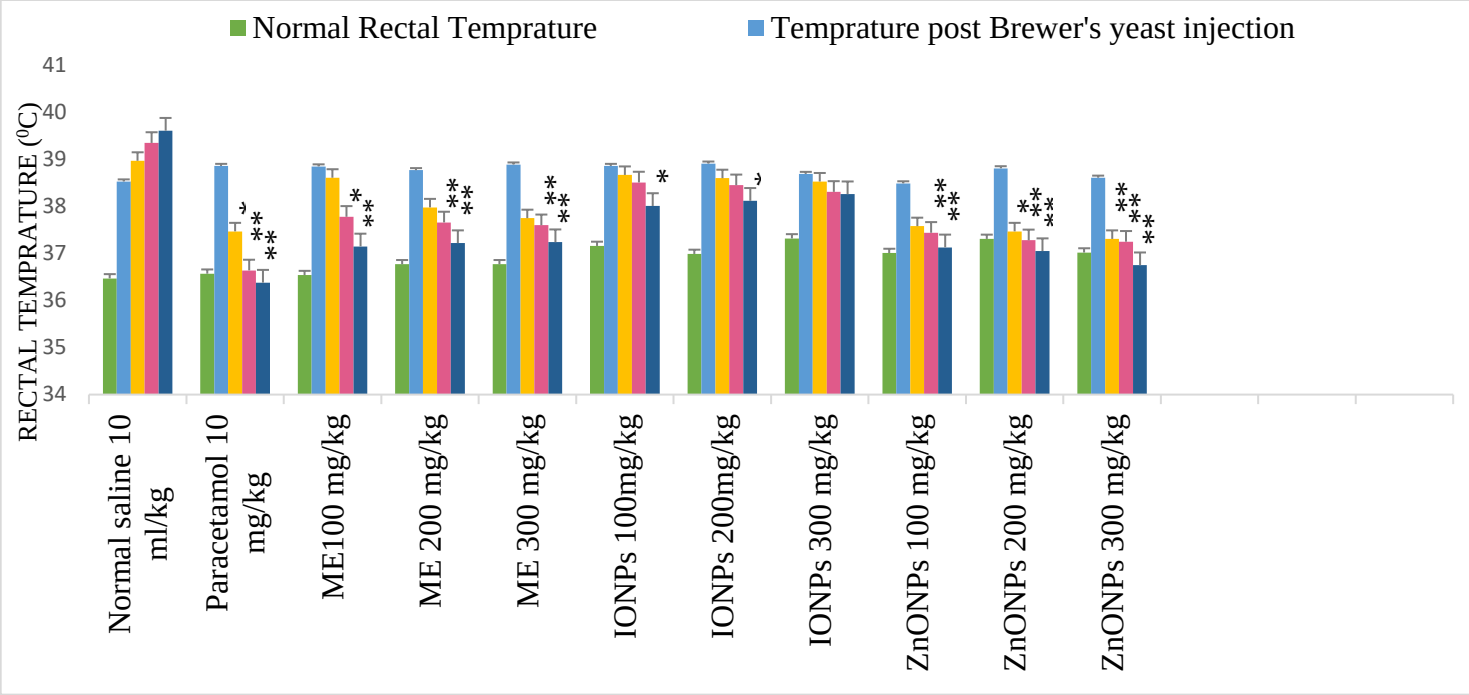

Fig.3. Mean change in body temperature (Pyrexia) of mice by *E. dracunculoides* methanolic fraction, iron oxide nanoparticles and zinc oxide nanoparticles at different time interval and doses. (*P < 0.05, considered significant) (p < 0.01, Highly Significant).**

Keywords: ME; methanolic extract, IONPs: Iron oxide nanoparticles, ZnONPs: Zinc oxide nanoparticles

Discussion

The current study for the first time reported that zinc oxide and iron oxide nanoparticles extracted from the methanolic fraction of *Euphorbia dracunculoides* are antibacterial agents, safe for human consumption, and antipyretic agents.

Some basic metabolites, including organic acids, amino acids, and peptides, as well as a wide range of secondary phytometabolites, such as tannins, flavonoids, alkaloids, coumarins, terpenes,

organosulfur compounds, carotenoids, phenolic acids, have antibacterial effects (Adamczak *et al*., 2020). The antibacterial activity of *E. dracunculoides* is attributed to phenolic compounds, alkaloids, and flavonoid compounds found in the plant extract. Plant-derived metallic nanoparticles showed additive antibacterial properties than extract alone. Antibiotic resistance in bacteria is a critical clinical concern in public health today, thus researchers are looking for novel antibiotics from a variety of sources. Recent advances in nanotechnology have laid the basis for the evolution of new antibacterial agents (Lalitha *et al*., 2012).

Zinc oxide nanoparticles are among the most analyzed inorganic metal oxides. This is assigned to its antibacterial properties, low toxicity to human beings, and its stability under harsh conditions. Many studies revealed that zinc oxide nanoparticles are very effective against various microbes and also prevent the biofilm formation of bacteria (Ifeanyichukwu *et al*., 2020). Scientists suggested that nanoparticles attach to the surface of the plasma membrane of bacteria through electrostatic forces. This attachment distorts the structure of the plasma membrane and loses the integrity of bacterial cells resulting in intracellular protein contents leakage which leads to the death of bacteria (Jayaseelan *et al*., 2012).

In addition, the disruption of membrane and cellular function is due to hydrogen bonding, van der wall forces, dipole-dipole, hydrophobic and electrostatic interaction (Rufus *et al*., 2016). Among other metal oxides, iron oxide nanoparticles possess unique properties and have tremendous biomedical applications for drug delivery and antibacterial properties. The toxicity of iron oxide nanoparticles inhibiting the growth of various bacterial strains (Madubuonu *et al*., 2020) Other researchers, Sheel *et al*., (2020) produced Magnetic iron oxide nanoparticles from *Phyllanthus niruri* and determined that they were effective against both Gram-positive and Gram-negative bacterial strains, and they demonstrated the highest antibacterial efficiency. Ramalingam *et al*., (2019) came up with similar results. Sharmila *et al*., (2018) created zinc oxide nanoparticles mediated by *Bauhinia tomentosa* leaf extract and tested their antibacterial properties against gram-positive and gram-negative. The results were compared with the results obtained by Chandra *et al*., (2019) and Pillai *et al*., (2020). Pati *et al*., (2014) and demonstrated that zinc oxide nanoparticles exhibit dose-dependent antibacterial activity. As a result, the antibacterial nature of zinc oxide/iron oxide nanoparticles may be shown in biomedical applications.

Plant extract and its nanoparticles are safe for the preparation of drugs and human consumption due to their toxicological study.

Antipyretic activity is a feature of drugs or compounds that block prostaglandin production, and it is a helpful test for screening plant materials and synthesized medicines for their antipyretic potential (Muhammad *et al*., 2012). The suppression of prostaglandin production, similar to that of paracetamol, might be a valid explanation for the antipyretic effect, and prostaglandin inhibition can be done by inhibiting the cyclooxygenase enzyme activity (Rauf *et al*., 2014). Antipyretic and antiplasmodial activity has been linked to the presence of alkaloids, glycosides, tannins, and flavonoids, which might be due to a single, additive, or synergistic effect of these substances(Okwu and Okwu, 2004, Trease and Evans, 1989). The antipyretic effects of plant extract and nanoparticles could be due to pharmacologically active metabolites increasing the production of the body's antipyretic substances like vasopressin and arginine, or to a reduction in brain concentrations of prostaglandin E2, especially in the hypothalamus, through their action on COX-3. These antipyretic drugs have been shown to lower proinflammatory mediators, enhance anti-inflammatory signals at injury sites, and boost antipyretic messages in the brain (Khan, 2017). These findings point to active components in plant extracts inhibiting prostaglandin production more effectively or similarly. As a result, there's a chance that the plant extracts are efficient in reducing fever by blocking alternate pathways.

Conclusion

This study summarized that both nanoparticles are safe for human consumption and the preparation of drugs.

Declaration of competing interest

All authors declare no conflict of interest in submission of this manuscript

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