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ANTIPYRETIC ACTIVITY OF UNRIPE PULP EXTRACTS OF *CUCUMIS SATIVUS*

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ABSTRACT
The main objective of the study is to evaluate antipyretic activity of aqueous, ethanol and ethyl acetate extracts of unripe pulp of *Cucumis sativus,* family *Cucurbitaceae* in experimental animals. *Cucumis sativus* commonly known as wild cucumber. The fruit of which is mainly consumed as a vegetable and non-toxic natural therapeutic agent used in various diseases. The preliminary phytochemicals investigations of extracts of *Cucumis sativus* unripe pulp was performed for the identification of carbohydrates, proteins, alkaloids, saponins, tannins, glycosides and triterpenes. Antipyretic effect of extracts of unripe pulp of the *Cucumis sativus* was investigated by milk induced Pyrexia method. Intraperitoneal administration of boiled milk at a dose 0.5 ml/kg body weight in albino rabbit leads to Pyrexia. In antipyretic activity oral administration of all the extracts at a dose 250, 500 mg/kg body weight were shown significantly reduce the elevated body temperature of rabbits which was compared with standard Paracetamol and control. The results shown that aqueous and ethanol extracts at 200, 500 mg/kg body weight shown significant ($p<0.05$) when compared to control. Aqueous extract is more significant compared to other all extracts. The interpretation of the result was done after subjecting the data obtained from various studies to appropriate statistical analysis which included one-way ANOVA followed by Dunnett's Multiple Comparison Test.

KEYWORDS: *Cucumis sativus,* Aqueous, Ethanol, Ethyl acetate, Rabbit, and Pyrexia.

INTRODUCTION
Nature is a wonderful and beautiful creation of great almighty, which has bestowed with many treasures for the use of mankind. Medicinal and aromatic plants, since times immemorial, have been used in virtually all cultures as a source of medicine. The use of traditional medicine and medicinal plants in most developing countries, as a normative basis for the maintenance of good health. Health is no longer defined simply in physical terms, as the absence of disease or disability, but now includes mental and social dimensions.[1] According to WHO report nearly 70-80% of world population relies on traditional medicine, largely plant based for primary health care needs. Traditional medicine is at the present time accepted as an alternative or used in conjunction with the western medicinal practices in many countries. India has much diversity of medicinal plants available in different regions. Approximately 90% of herbal raw drugs used in the manufacture of *Ayurveda, Siddha, Unani and Homeopathy* systems of medicines.

India is known for its rich biodiversity and legacy of traditional wisdom. While traditional medicine has long used herbal extracts on patients, reverse pharmacology is aimed at validating such extracts through rigorous science.[2] It takes the reverse route of clinical safety and efficacy validation of healthcare product originally based on traditional knowledge and experience. Revival of herbal medicines and their usage in new light will be the next medical evolution.[3] Since the primeval time man is trying to find the sources in order to preserve the health, synthetic and natural products are the sources from which most of the pharmaceutical and biological agents

are derived. The plants are indispensable to man for his life. food, clothing and shelter are considered important necessities of life and are supplied to human by plant kingdom.

Cucumber is scientifically named as *Cucumis sativus*. It is a widely cultivated plant in the gourd family *Cucurbitaceae* and genus *Cucumis*. The fruit is roughly cylindrical, elongated, with tapered ends, and may be as large as 60 cm long and measuring 10 cm in diameter. *C. sativus* are eaten fresh and pickled. Cucumber is a source of many chemical constituents. It contains carbohydrates, sugar, proteins, fats, and dietary fibers. It is an excellent source of vitamin C, folic acid and potassium. A cucumber contains usually more than 90% of water. The skin of cucumber is rich in fiber that contains variety of minerals such as potassium, magnesium and silica. It is a great source of minerals such as iron, manganese, phosphorous, calcium, zinc, pantothenic acid, niacin, riboflavin, thiamine, and folate.[5] Cucumber possesses many medicinal properties such as diuretic, cooling and cleansing in action. Cucumber is best natural diuretic known, secreting and promoting the flow of urine. It also helps in kidney and urinary bladder disease. Fresh cucumber juice can provide relief from heartburn, acid stomach, gastritis and ulcer. Consumption of cucumber juice helps to control cases of eczema, arthritis and gout.[6] Cucumber has been found to be beneficial for those suffering from lung, stomach and chest problems. The potassium in cucumber makes it useful for the problem of high and low blood pressure. Cucumber is said to be good for rheumatic conditions caused by excessive uric acid in the body. Cucumber has been associated with healing properties in relation to diseases of the kidney, urinary bladder, liver and pancreas. People suffering from diabetes mellitus have been found to benefit from the consumption of cucumber.[7] Cucumbers provide us with a variety of health supportive phytonutrients. The aim of the present study is to investigate the antipyretic activity of the extracts of unripe pulp of *Cucumis sativus.*

MATERIALS AND METHODS

Plant Collection and Identification

Fresh *Cucumis sativus* (Cucumber) was collected from the farms at Magadi, Ramanagar, Karnataka, India and authenticated by Prof. Nagaraj H department of Botany, Bharathi college, Bharathinagar, Karnataka, India. Fresh tender unripe fruits before developing seeds were selected. This is homogenized and dried under shade and thus dark brownish red powder mass obtained. The dried *C. sativus* fruit pulp was reconstituted in water, the extract so obtained, was subjected to qualitative phytochemical analysis.

Preparation of Extract

About 200gms of dry powder of unripe pulp of *Cucumis sativus* was successively extracted with ethyl acetate (60-70^{0}C) 72 hrs ethanol and aqueous. The extract was concentrated and dried using Rotary vacuum evaporator and kept in a desiccators until used.

Qualitative Phytochemical Screening of Extracts

Phytochemical analysis of the extracts was carried out by the standard methods to detect various phytoconstituents present in the extracts of *Cucumis sativus*.[11]

Acute Oral Toxicity Studies

Acute oral toxicity test was performed as per Organization for Economic Co-operation and Development (OECD) guidelines 423.[12] The institutional ethical committee of Bharathi College, Bharathinagara, Karnataka, India. Experiments were performed using healthy young adult female Swiss albino mice, nulliparous, non-pregnant and weighing 25-30g. Female mice were chosen because of their greater sensitivity to treatment.[12]

Test Animals

Healthy adult rabbits were used for this study. The animals were housed individually in an area of uniform temperature (±2 °C) with uniform humidity and free from disturbances to excite them. The animals are given *ad libitum* water and food. First three days before using an animal that has not previously been used for a pyrogen test, condition it by conducting a training exercise omitting the injection. After a pyrogen injection in the course of which a rabbit's temperature has risen by 0.5°C or more. The experiment was carried out on albino rabbits. They were 13-15 months old of both sexes weighing between 1.5-1.6 kg.[13,16] They were collected from the Bharathi College. The rabbits were kept in iron cages[13] (considering group), were fed with cauliflower, cabbage, banana and tap water for 40 days before experiment to adjust with environment. Food and water were withdrawn 6 hours prior to the experiment. The study protocols were duly approved by the Institutional Animal Ethics Committee (IAEC) of Bharathi College, Bharathinagara, Karnataka India. Studies were performed in accordance with the CPCSEA guidelines.

ANTI PYRETIC ACTIVITY

(Milk Induced Pyrexia Method)

In this procedure milk is used as a pyrogen and injected subcutaneously with the dose of 0.5 ml / 100gms body weight. It induces pyrexia in 2-3 hrs. This method is adopted if the experimental animals are albino rabbit. The subcutaneous injection of milk is known to produce fever in albino rabbit. A decrease in temperature can be achieved by administration of compounds with antipyretic activity. The main aim of the experimental study was to evaluate antipyretic activity of *Cucumis sativus*. Behaviour observational study of albino rabbits before and after induction of pyrexia.

Collection and Preparation of Milk

Healthy adult albino rabbits were selected for this milk induced pyrexia method. Milk was collected from local cow and boiled and equilibrates to room temperature.

The rabbits were injected boiled milk at the dose of 0.5 ml/kg body weight, to induce pyrexia. Induction of fever was taken about one to two hours.[14]

Temperature Recording

Use an accurate thermometer graduated in 0.1^0C that has been tested to determine the time necessary to reach the maximum reading, or any other temperature recording device of equal sensitivity. Insert the temperature sensing device into the rectum of the test animal to a depth of about 6 cm. If the temperature sensing device is to remain inserted throughout the sensing period, restrain the rabbit with a lightly-fitting neck stock that allows it to assume a natural resting posture. When a thermometer is used, allow sufficient time for it to reach a maximum temperature, as previously determined, before taking the reading. In the present study digital thermometer was used.

Table 1: Grouping of animals for Antipyretic activity.

Groups	No. of animals used	Drug	Dose
Group I	3	Dist water	2ml/rabbit
Group II	3	Paracetamol	10mg/kg
Group III	3	Test ACSELD	250mg/kg
Group IV	3	Test ACSEHD	500mg/kg
Group V	3	Test ECSELD	250mg/kg
Group VI	3	Test ECSEHD	500mg/kg
Group VII	3	Test EACSELD	250mg/kg
Group VIII	3	Test EACSEHD	500mg/kg

ACSELD= Aqueous *Cucumis sativus* Linn low dose extract
ACSEHD= Aqueous *Cucumis sativus* Linn high dose extract
ECSELD= Ethanol *Cucumis sativus* Linn low dose extract
ECSEHD= Ethanol *Cucumis sativus* Linn high dose extract
EACSELD= Ethyl acetate *Cucumis sativus* Linn low dose extract
EACSEHD= Ethyl acetate *Cucumis sativus* Linn high dose extract.

Pre-Experimental Setup

Perform the test in the area where the animals are housed or under similar environmental conditions. For 2 hrs before the test and during the test, withhold all food from the animals being used. Access to water may be allowed. The animals should be placed under the conditions of the test at least 1 hour before the injection. Prior to the test, before the injection of the test material, determine the temperature of each animal by taking two measurements at an interval of 30 minutes. The mean of the two temperatures serves as the "control temperature" of the animal. The control temperature recorded for each rabbit constitutes the temperature from which any subsequent rise following the injection of the material is calculated.

Duration: 24 hrs, all the experiments were conducted in the same climatic conditions.

Injection Technique

Intraperitoneal (IP) injection: Hold the rabbit ventral side up, grasping the skin over the nape of the neck and rump. Enter the needle on a 45 degree angle in the lower quadrant of the abdomen aspirate to insure needle placement does not occur into an intestine, urinary bladder or blood vessel.

PROCEDURE

The antipyretic activity of the aqueous, ethanol and ethyl acetate extract of *Cucumis sativus* was screened by using milk induced hyper pyrexia method. A group of 3 experimental rabbits having average weight of 1.5-1.6 kg were taken on the day of the study food was withheld and rabbit was acclimatized to the test condition for 2 hrs, the base line temperature was recorded initially half an hour prior to injection. Before the experiment, rectal temperatures of the rabbits were recorded by inserting a well lubricated bulb of a thermometer in to the rectum. Care was taken to insert it to the same depth each time about 6 cm.[14] Milk was collected from local cattle. Rabbits were injected with boiled milk at room temperature at the dose of 0.5 ml/kg body weight to induce pyrexia. Induction of fever took about 1 to 2 hrs.[14,15] After injection of pyrexia a significant increase in temperature (±5) from basal value are observed were regarded as hyperthermia. Does the test and standard drugs are dissolved in distilled water were administered orally to the rabbit in all groups respectively. The post drug treatment rectal temperature of each rabbit was recorded at a time point 1, 2 and 3 hrs. The differences in temperature before and after the administration of extracts and Paracetamol were recorded and evaluated the antipyretic activity of *Cucumis sativus* extracts.[15,16,17]

STATISTICAL ANALYSIS

The results data was expressed as mean value ± SEM. Statistical comparison analysis carried out by using one way ANOVA was done with PRISM.5 software and the difference between mean of treated groups and the non treated control group was evaluated by the Dunnett's multiple comparison test. The result was considered statistically significant when P values < 0.05.

RESULTS

Extraction

Wet weight of the collected unripe pulp of *Cucumis sativus* was 8 kg and the dry weight was found to be 1kg. Practical yield of ethyl acetate, ethanol and aqueous obtained was 20, 100, 50gm respectively. The percentage yield of aqueous, ethanolic and ethyl acetate extract of *C.sativus* was found to be 2,10 and 5% w/w respectively.

Phytochemical Constituents Present in Aqueous, Ethanol and Ethyl Acetate Extract of *Cucumis Sativus*

The extracts was subjected to qualitative chemical analysis for the identification of various phytoconstituents. The results of the chemical tests was recorded and tabulated in the following Table-2.

Table 2: Details of Qualitative Phytochemical tests of Extracts.

Phyto-constituents / Tests	ACSE	ECSE	EACSE
Carbohydrates			
Molish's Test	+	+	+
Fehling's test	+	+	+
Benedict's Test	+	+	+
Proteins			
Millon's Test	+	+	+
Ninhydrin test	+	+	+
Alkaloids			
Mayer's Test	+	+	+
Wagner's Test	+	+	+
Dragendroff's Test	+	+	+
Tannins and Phenols			
5% Ferric chloride solution	_	_	_
Lead acetate test	_	_	_
Flavonoids			
Aq. Sodium hydroxide test	_	_	_
Sterols			
Salkowski's test	_	_	_
Saponins			
Froth test	+	+	+
Glycosides			
Legal's test			
Modified	+	+	+
Borntrager's test	+	+	+
Triterpenoids			
Salkowski	+	+	+

Presence (+), Absence (-)

The results of phytochemical screening showed the presence of carbohydrates, proteins, alkaloids, triterpenoids, saponins and glycosides.

Acute Oral Toxicity

The 3 extracts did not produce any mortality throughout the study period of 28 days even when the limit dose was maintained at 5000 mg/kg body weight. The oral LD_{50} was indeterminable being in excess of 5000 mg/kg body weight. So, testing the extracts at a higher dose may not be necessary and the extracts were practically non-toxic.

Table-3: indicates the parameters observed before and after the administration of the three extracts of *Cucumis sativus*. All the parameters observed were normal even at the highest dosage of 5000 mg/kg body weight of the test animal. This clearly indicated that the 3 extracts of *Cucumis sativus* did not produce oral toxicity. So the therapeutic dose for the pharmacological evaluation by CSE was 1/10th of the maximum tolerated dose which was then fixed to be 250 and 500 mg/kg of the experimental animal for the further studies.

Table 3: Effect of *Cucumis sativus* extracts on acute oral toxicity test in mice.

RESPONSES	ACSE	ECSE	EACSE
Alertness	N	N	N
Grooming	A	A	A
Touch response	P	P	P
Torch response	P	P	P
Pain response	P	P	P
Convulsion	A	A	A

Corneal reflux	P	P	P
Pupils	N	N	N
Urination	N	N	N
Skin colour	N	N	N
Lacrimation	A	A	A
Hyper activity	A	A	A
Weight	N	N	N

N- Normal, P-Present, A-Absent

Antipyretic Activity

There was significant reduction in rectal temperature of rabbits.

Table 4: Rectal temperature before & after drug administration.

Groups	Dose	Rectal temperature (ºC)		Rectal temperature after treatment (ºC)		
		Before induction (A)	3 Hours after Induction (B)	1hr	2hr	3hr
Control	2ml/rabbit	101.2±0	104.3±0.058	104.1±0.058	104±0	104±0
Paracetamol	10mg/kg	101.5±0.058	104.2±0.058	103±0.058***	101.5±0.115	101.5±0.058
ACSELD	250mg/kg	101.3±0.058	104.3±0.058	104.1±0.058	101.7±0.252	101.4±0.100
ACSEHD	500mg/kg	101.4±0.058	104.6±0.153	103.3±0.153***	103.3±0.173	101.9±0.100
ECSELD	250mg/kg	101.6±0.115	104.6±0.058	103.7±0	102.5±0.058	102.2±0.058
ECSEHD	500mg/kg	101.8±0	104.3±0.115	103.8±0.058	103.3±0.10	103.1±0.153
EACSELD	250mg/kg	101.4±0.115	104.3±0.115	103.9±0	103.4±0.058	102.9±0.058
EACSEHD	500mg/kg	101.2±0.058	104.2±0.058	104±0	103.7±0.058	103.5±0.100

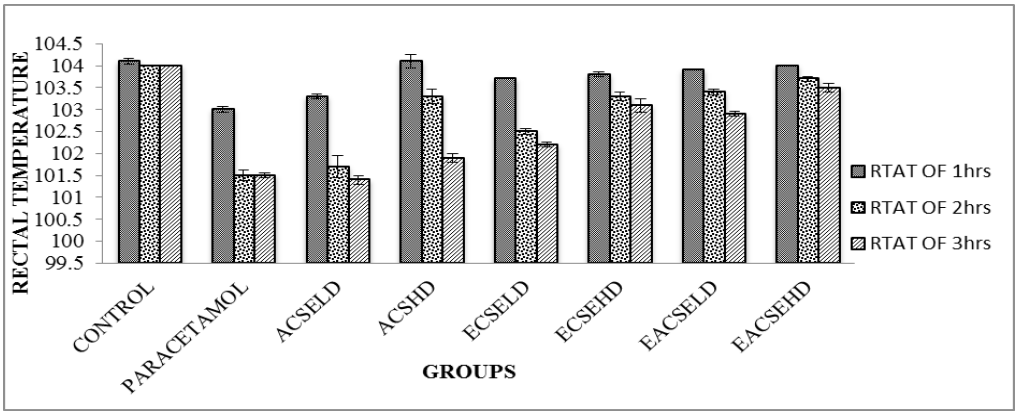

Fig.1: Graphical representation of Change in rectal temperature after drug administration per hour.

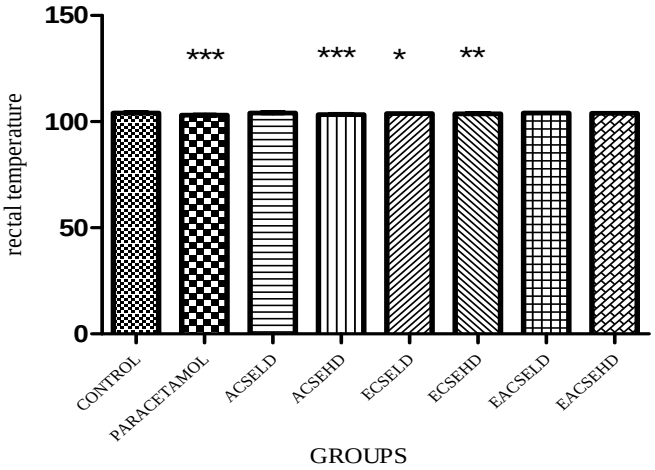

Fig.2: Graphical representation of Antipyretic effect of *C. sativus* extract in 1 hour after treatment.

Each bar represents rectal temperature in 1 hour. The values were expressed in Mean± SEM. n=3. * represents P<0.05 when compared with Control. ** represents P<0.01 when compared with Control.*** represents P<0.001 when compared with Control.

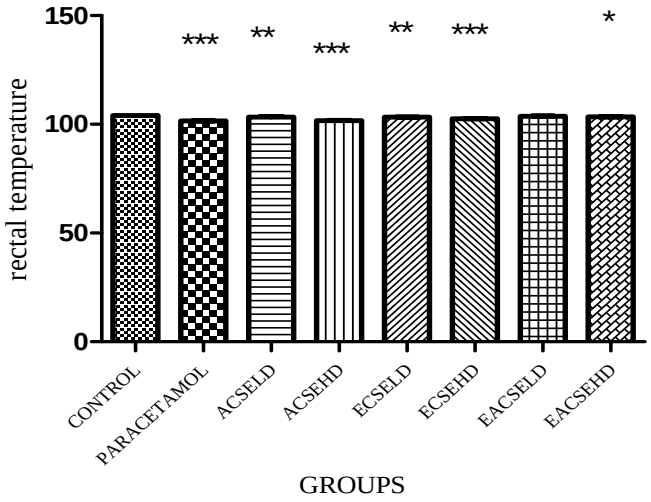

Fig.3: Graphical representation of Anti-pyretic effect of *C. sativus* extract in 2 hours after treatment.

Each bar represents rectal temperature in 2 hours. The values were expressed in Mean± SEM. n=3. * represents P<0.05 when compared with Control. ** represents P<0.01 when compared with Control.*** represents P<0.001 when compared with Control.

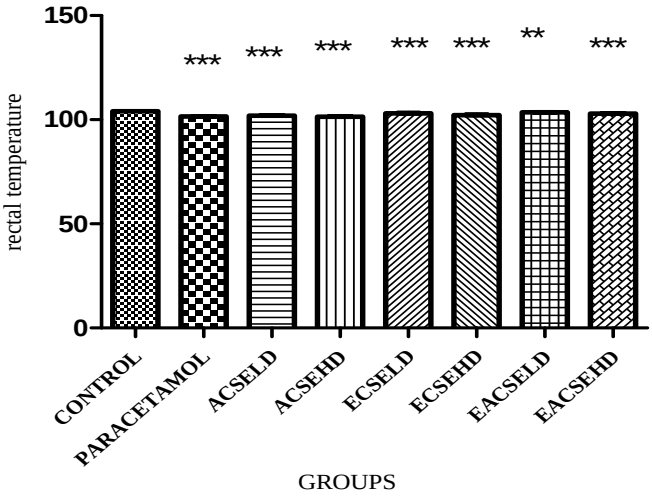

Fig.4: Graphical representation of Anti-pyretic effect of *C. sativus* extract in 3 hours after treatment.

Each bar represents rectal temperature in 3 hrs. The values were expressed in Mean± SEM. n=3. * represents P<0.05 when compared with Control. ** represents P<0.01 when compared with Control.*** represents P<0.001 when compared with Control.

Table 5: Percentage Reduction in Temperature per hour.

Groups	% Reduction of temperature in 1 hr	% Reduction of temperature in 2 hr	% Reduction of temperature in 3 hr
Control	6.45	9.67	9.67
Paracetamol	44.44	100	100
ACSELD	6.66	86.66	96.66
ACSEHD	40.62	40.62	84.37

ECSELD	30	70	80
ECSEHD	20	40	48
EACSELD	13.79	31.03	48.27
EACSEHD	6.66	16.66	23.33

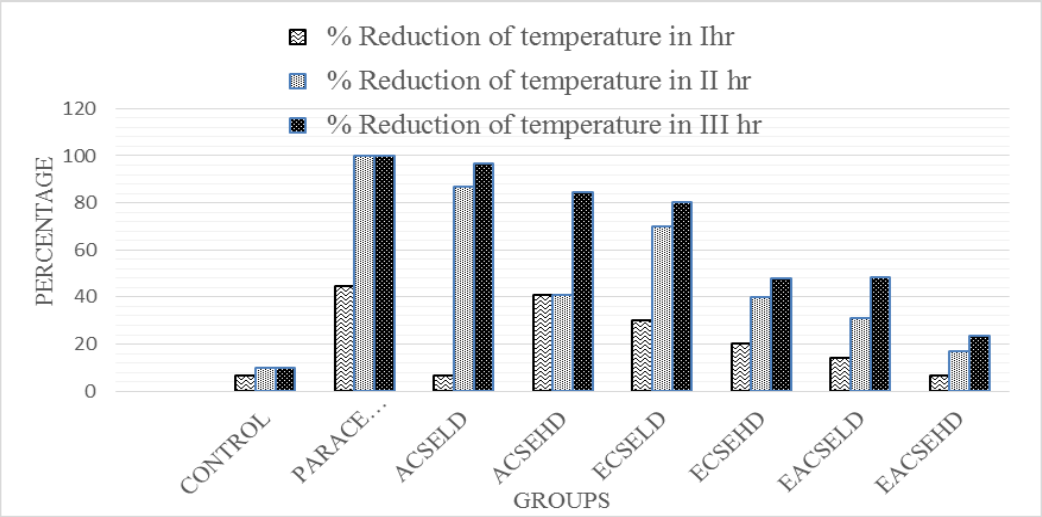

Fig. 5: Graphical representation of Percentage Reduction in Temperature per hrs.

Behaviour Observations in Animals

Table 6: Behaviour Observations before and after the induction of Pyrexia in Animals.

Sl. No.	Observations	Before the induction of Pyrexia	3 hrs after induction of Pyrexia
1	Temperature	Normal body temperature	Raised body temperature above normal when felt with touch
2	Activities	More active	Decreased activities
3	Behaviour	Normal with good food and water intake	Dull looking, Face bent downwards Looking tired, Scanty micturition

DISSCUSION

Cucumbers are an excellent source of anti-inflammatory vitamin K. They are also a very good source of the enzyme-cofactor molybdenum. They are also a good source of free radical-scavenging vitamin C; heart-healthy potassium and magnesium, bone-building manganese, and energy-producing vitamin B_5. They also contain the important nail health-promoting mineral silica and phytonutrients like triterpenes (Cucurbitacin A, Cucurbitacin B, Cucurbitacin C, Cucurbitacin D, Cucurbitacin E). Cucumbers are a valuable source of conventional antioxidant nutrients including vitamin C, beta-carotene, and manganese. Fresh extracts from cucumber have been shown to provide specific antioxidant benefits, including increased scavenging of free radicals and increased overall antioxidant capacity. Cucumber accomplishes this task by inhibiting activity of pro-inflammatory enzymes like cyclo-oxygenase 2 (COX-2), and by preventing overproduction of nitric oxide in situations where it could increase the likelihood of excessive inflammation.

The non-toxic nature of extracts of *Cucumis Sativus* is evident by the absence of mortality of the test animals at oral treatment of 5000 mg/ kg body weight. *Cucumis sativus* contains saponin, triterpienoides, in particular glycoalkaloids, which are found in all parts of the plant. The non-toxic nature of extracts of *Cucumis sativus* reveals the non-toxic nature of the foresaid phytochemicals at the tested dosage. Hence extracts of *Cucumis sativus* may be exploited for its use in product application like pharmaceuticals/ nutraceuticals/ cosmeceuticals. The oral non-toxic nature of the plant and the use of this plant go hand in hand with scientific evidence provided by the study. Phytochemical screening revealed the presence of alkaloids, triterpenoids, carbohydrates, proteins, saponins, and glycosides. Different activities observed in the crude extract might be due to the presence of these phytochemicals. For example, alkaloids and triterpenoids are known to, antioxidant and diuretic activities. Glycosides are known to cardiac active.

Antipyretic activities of extracts may be due to the presence of alkaloids, triterpenoids and. 1, 2 and 3 hours after administration of the plant extract (*Cucumis sativus*) as well as the standard (Paracetamol) body temperature declines. This decline in case of *Cucumis sativus* was not as sudden as Paracetamol administration and therefore, can be considered more suitable. It is also evident from the study that the antipyretic activity of aqueous extract at 500 mg/kg body weight is almost similar to the standard group and is more active than the test extracts.

The resultant effects of all extracts of *Cucumis sativus* on boiled milk induced pyrexia in rabbits are depicted in Table-4. At a dose of 250 mg/kg body weight, aqueous, ethanolic and ethyl acetate extract reduced 84.37%, 48% and 23.33%, respectively after 3hrs of treatment, of elevated rectal temperature compared to Paracetamol (100% after 3 hrs). At a dose of 500 mg/kg body weight, aqueous, ethanolic and ethyl acetate extracts reduced 96.66, 80.0 and 48.27%, respectively, of elevated rectal temperature compared to Paracetamol (100% after 3 hrs). One way ANOVA followed by Dunnett's analysis for Urine output 24 hrs./rabbit between the groups at 95% confidence interval or The values were expressed in Mean± SEM. n=3. * represents P<0.05 when compared with Control. ** represents P<0.01 when compared with Control. *** represents P<0.001 when compared with Control. The antipyretic activity after 3rd hrs results when compared with Control group and Standard, **'P'** value was 0.001 showed statistically highly significant when compared Control group and Trial group ACSELD, ACSEHD, ECSELD, ECSEHD, EACSEHD showed **'P'** value was 0.001 statistically highly significant like standard. And Trial group EACSELD **p<** 0.01 showed statistically significant when compared with Control. Thus all aqueous, ethanolic and ethyl acetate extracts produced significant (P < 0.05) antipyretic effect at 250, 500 mg/kg and when compared to control all extracts produce significant activity in reduction of temperature 3hrs after the treatment of trial drugs. Out of this aqueous extract produce more active and its results might comparable with standard. It was also observed that the solvent have no effect on the reduction of pyrexia of rabbit.

Research article shows that aqueous extracts of *Cucumis sativus* have proper efficacy on wound healing.[18] Therefore, the antipyretic activity of extracts of *Cucumis sativus* is probably by inhibition of prostaglandin synthesis. Phytochemical screening revealed the presence of alkaloids, triterpenoids, carbohydrates, proteins, saponins, and glycosides. Therefore the reason for anti pyretic activity might be alkaloids, saponins, glycoside and triterpenoids.

CONCLUSION

On preliminary phytochemical screening of unripe pulp extracts of *Cucumis sativus* showed the presence of carbohydrates, proteins, alkaloids, triterpenoids, saponins and glycosides. The presence of these compounds offers antipyretic activity. The non-toxic nature of extracts of *Cucumis sativus* is evident from the acute oral toxicity conducted as per OECD guidelines. The normal behavior of the test animals during a period of 28 days suggests the non-toxic nature of the foresaid extracts. Hence *Cucumis sativus* could be safe up to the dose of 5000 mg/kg body weight of the animal. Further studies are warranted for determining chronic toxic symptoms. The extract of *Cucumis sativus* has antipyretic effect supporting the ethno pharmacological use as antipyretics. This effect may be explored in the use of the plant in the management of some other diseases. The antipyretic activity observed can be attributed to the presence of saponins, glycosides, triterpenoids and alkaloids have been reported to exhibit antipyretic effect. However, further investigation is required to isolate the active constituents responsible for these activities and to elucidate the exact mechanism of action. The present study confirms the claims of traditional medicine practitioner's antipyretic remedy.

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