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Preclinical assessment of analgesic, anti-inflammatory and antipyretic potential of *Fragaria ananassa* and *Actinidia deliciosa* fruit extract

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Abstract: *Fragaria ananassa* (garden strawberry) and *Actinidia deliciosa* (kiwi) fruits are widely consumed due to their taste and nutritive value however several studies also supports their medicinal uses. Current study was designed to assess the *In-Vivo* analgesic, anti-inflammatory and antipyretic activity of ethanol extract of *Fragaria ananassa* (EEFA), *Actinidia deliciosa* (EEDA) and their 1:1 combination. Albino Wistar rats were divided into five groups (n=5) for each study comprising of vehicle control, reference standards *(aspirin and paracetamol 100 mg/kg/day), EEFA (800 mg/kg/day), EEAD (800 mg/kg/day) and 1:1 combination of EEFA and EEAD (400 + 400mg/kg/day). The results revealed significant anti-inflammatory potential of EEAD and their combination with 79.35% and 82.03% inhibition in carrageenan induced paw edema whereas 52.54% inhibition was produced by EEFA against control. However most powerful analgesic effect was produced by EEFA with 52.23% at 60 min followed by EEAD (48.38%) and EEFA+ EEAD combination (44.09%). Similarly, EEFA, EEAD and their combination also lowered the rectal temperature in highly significant manner ($p \leq 0.01$) against control. These results suggested the possible role of garden strawberry and kiwi in treating the ailments related to pain, inflammation and fever however further studies are required to elucidate the constituents responsible for it and their exact mechanism.

Keywords: *Fragaria ananassa, Actinidia deliciosa* anti-inflammatory, analgesic, antipyretic activities, EEFA and EEAD

INTRODUCTION

For centuries, herbal medicines are representing their significant role in health care system. From ages, herbal drugs were found to be the most consistent source for progression of new medicines because of a number of bioactive molecules like alkaloids, glycosides, flavonoids, terpenes and phenolic moieties. Certain plant species rich in phenolic contents presents their auspicious role in the field of research possibly due to their antioxidant properties. However, among them berries are playing their remarkable role in health care system.

Fragaria ananassa commonly known as strawberries belongs to the family *Rosaceae*. Strawberries can be taken as a healthy choice with respect to the occurrence of phytochemicals including tannins, flavonoids, alkaloids, minerals and anthocyanins (Aaby K *et al.*, 2005; Giampieri *et al.*, 2012; Samia *et al*., 2019). Many researchers have identified the nutritious as well as medicinal properties of *F. ananassa* fruits and established their safe use against various ailments and pathologies such as cancer, cardiovascular disorders, diabetes, obesity and numerous infections (Cheplick *et al.*, 2010; Pinto Mda *et al.*, 2010; Abdulazeez, 2014). However, in order to improve the shelf life strawberries can be stored in processed form such as juices, jams, nectars as well as in frozen form to retain their phytochemical contents. Moreover, strawberries have been used in the prevention of oxidative stress induced skin diseases as well as play beneficial role in reducing the risk of cardiovascular disorders (Duttaroy & Jorgensen, 2004; Iwasawa *et al.*, 2011).

Chinese gooseberry or kiwi (*Actinidia deliciosa)* belongs to *Actinidiaceae* family. The fleshy fruits of kiwi are oval spherical in shape with edible seeds having pleasant taste (Saliyan *et al.*, 2017). However, the juice of kiwi fruit retains the highest percentage of phenolic contents showing highest antioxidant properties (Dawes & Keene, 1999).

Now a days, use of natural and herbal originated product to prevent or manage different aliments is gaining popularity all over the world. This approach is considered more holistic, safe, economical and widely accepted all over the world, therefore present study was designed to explore the potential of *Fragaria ananassa* and *Actinidia deliciosa* fruits ethanol extracts and their combination for the management of inflammation, pain and pyrexia using experimental models.

MATERIALS AND METHODS

Drugs and chemicals

Aspirin (300 mg) of Reckitt Benckiser Pakistan limited and Paracetamol (500mg) of GlaxoSmithKline (GSK) were obtained from local market. All other chemicals

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required for the study were of analytical grade from Merck.

Collection and identification of fruits

The fruits of *Fragaria ananassa* and *Actinidia deliciosa* were purchased from local market and were identified and authenticated by Dr. Mohtesheem ul Hassan, Department of Pharmacognosy, Faculty of Pharmacy and Pharmaceutical Science under the voucher number FAF-06-19 for *Fragaria ananassa* and ADF-05-19 for *Actinidia deliciosa* respectively.

Extract preparation

Exactly 0.5kg fruits of both *Fragaria ananassa* and *Actinidia deliciosa* were soaked in 2 liters of 70% ethanol in two separate jars for 48 hours with occasional shaking after every 2 hours then filtered through filter paper. The filtrate obtained was concentrated in rotary evaporator while the extracts were kept under refrigeration at 6-8˚C before the start of experiment.

Animal selection and housing

Albino Wistar rats weighing 140-200gm of both sexes were purchased from the animal house of Hussain Ebrahem Jamal Institute of Chemistry (H.E.J), University of Karachi. All animals were acclimatizing for 5 days before the commencement of experiment. They were housed in plastic cages, in animal house of Department of Pharmacology, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi. Throughout the study period 12 hour light and dark cycle and ambient temperature of 25±2˚C was maintained. All the animals were provided with standard pelleted feed and water *ad libitum* for entire study period.

Group	Treatment
Group I	Distilled water 10 ml/kg/day orally
Group II	Aspirin 100 mg/kg/day orally (Babuselvam *et al.*, 2012)
Group III	Ethanol extract of *Fragaria ananassa* 800 mg/kg/day orally (Ibrahim & Abd El-Maksoud, 2015)
Group IV	Ethanol extract of *Actinidia deliciosa* 800 mg/kg/day orally (Soren *et al.*, 2016)
Group V	EEFA(400 mg/kg) + EEAD (400 mg/kg) orally (Ibrahim & Abd El-Maksoud, 2015; Nandini & Hari Kumar., 2017)

Experimental design and dosing

Anti-inflammatory and Analgesic Activity

Following groups were made simultaneously for anti-inflammatory and analgesic activity assessment comprising of 5 animals per group (n=5).

Antipyretic activity

Following groups were made for antipyretic model comprising of 5 animals per group (n=5).

Group	Treatment
Group I	Distilled water 10 ml/kg/day orally
Group II	Paracetamol 100 mg/kg/day orally (Akapa *et al.*, 2014)
Group III	Ethanol extract of *Fragaria ananassa* 800 mg/kg/day orally (Ibrahim & Abd El-Maksoud, 2015)
Group IV	Ethanol extract of *Actinidia deliciosa* 800 mg/kg/day orally (Soren *et al.*, 2016)
Group V	EEFA(400 mg/kg) + EEAD (400 mg/kg) orally (Ibrahim & Abd El-Maksoud, 2015; Nandini & Hari Kumar, 2017)

Anti-inflammatory activity

Carrageenan Induced Paw Edema

All animal groups were administered with the defined treatment one hour prior to sub-plantar injection of carrageenan to measure the inhibitory effects of both fruits against inflammation. Initial volume of right hind paw of all the animals were recorded by using plethysmometer (UGO Basile, Italy). Acute inflammation was induced through carrageenan injection (1% w/v) at a concentration of 0.1ml in right hind paw of rats however left paw was kept as negative control. The volume of paw edema for each rat was recorded every 1 hour till 4 hours following carrageenan injection. Percentage inhibition of test groups against control was calculated by using following formula (Meshram *et al.*, 2015):

$$PI = \frac{(V_t\text{-}V_o)\ \text{control} - (V_t\text{-}V_o)\ \text{treated}}{(V_t\text{-}V_o)\ \text{control}} \times 100$$

Where,

V_o = Mean paw volume at 0 hour

V_t = Mean paw volume at a particular time interval

Analgesic activity

Hot Plate Test

Each rat was introduced to hot plate analgesia meter maintained at a temperature of 55˚C within the restrainer (Eddy & Leimback, 1953). Animals that showed pain responses within 2 to 10 sec were included in the study. Reaction time (in seconds) or period of latency was recorded as time taken by rats in response to thermal stimuli by jumping or licking their paws at 0 min (before) and at 15, 30, 45 and 60 min after test and standard dose administration (Fan *et al.*, 2014). To avoid paws damage maximum 20 sec cut-off period was observed. Percentage inhibition of test groups and reference standard was obtained by using following formula (Gupta & Singh, 2017):

$$\% \text{ Inhibition} = (P_T\text{-}P_0) / (X\text{-}P_0) \times 100$$

Where, P_T = Post treatment latency

P_0 = Pre-treatment latency

X = cut –off time of 20 sec

Antipyretic activity

Boiled Milk Induced Hyperthermia

Female albino Wistar rats were kept in the food deprived condition 18 hours before the experimental conduction

with continuous provision of water. Rectal temperature was recorded for each rat before the commencement of study by using a well lubricated digital thermometer into the rectum. Thermometer should be inserted carefully with equal depth of 6cm for each time. Boiled cow milk (2ml/kg/day i.p.) was used to induce hyperpyrexia in rats when its temperature equilibrates to room temperature (Indumathy *et al.*, 2011). About one to two hours were taken to induce pyrexia in experimental rats. The rectal temperatures were recorded after 1, 2, 3 and 4 hours of dosing (Nisar *et al.*, 2008). Percent reduction in pyrexia was obtained by using following formula (Muhammad *et al.*, 2012);

Percent reduction = $B\text{-}C_n/B\text{-}A \times 100$

Where,

B = Temperature observed after induction of pyrexia

C_n = Temperature recorded after the interval of 1, 2, 3 and 4 h

A = Temperature recorded before treatment

Ethical approval

The current study was approved by Institutional Bioethical Committee, University of Karachi, under approval number IBC KU-90/19.

STATISTICAL ANALYSIS

Values are presented as mean ± SEM (n=5). Data was analyzed statistically by using IBM SPSS (version 24) one-way ANOVA followed Post hoc Tukey's test for multiple comparison. P≤0.05 and P≤0.01 were considered to be significant and highly significant respectively.

RESULTS

Anti-inflammatory activity

Results illustrated the acute anti-inflammatory activity of EEFA, EEAD and their combination by paw edema induced by carrageenan reported in table 1. The EEFA; EEAD combination and EEAD (800mg/kg/day) have showed significant effects in comparison to positive control aspirin however considerable anti-inflammatory has also been observed with EEFA (800mg/kg/day).

Analgesic activity

The results illustrated the analgesic activity of EEFA, EEAD and their combination by using hot plate method are presented in table 2. Post hoc Tukey test showed significant (P≤0.05) and highly significant (P≤0.01) increase in reaction time in time dependent manner at 15, 30, 45 and 60 min by treated groups as well as aspirin (reference standard) in comparison to negative control. Maximum analgesic activity was observed with EEFA with 52.23% increase in reaction time at 60 min which is far greater than the standard group reading at same time i.e. 32.53%. Similarly EEAD showed significant analgesic activity with 48.38% increase in reaction time at 60 min against control. Whereas EEFA+EEAD combination exhibit significant activity with a maximum of 44.09% increase in reaction time against control.

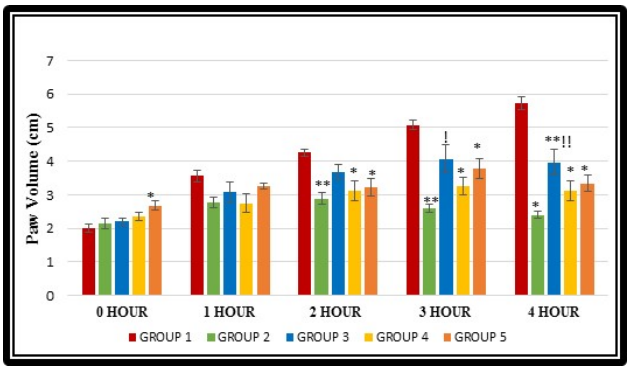

Fig. 1: Anti-inflammatory activity of ethanol extract of *Fragaria ananasssa* and *Actinidia deliciosa* by Carrageenan induced paw edema

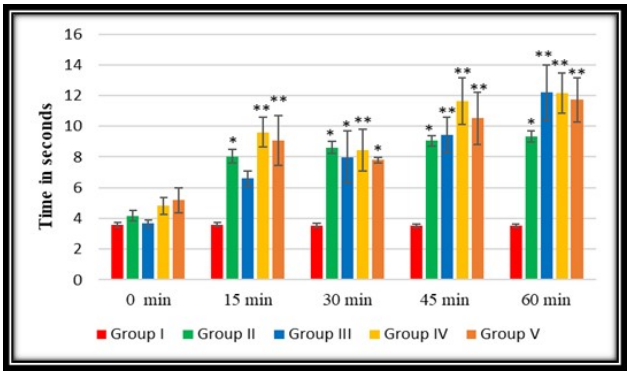

Fig. 2: Analgesic activity of ethanol extract of Fragaria ananassa and Actinidia deliciosa by hot plate method

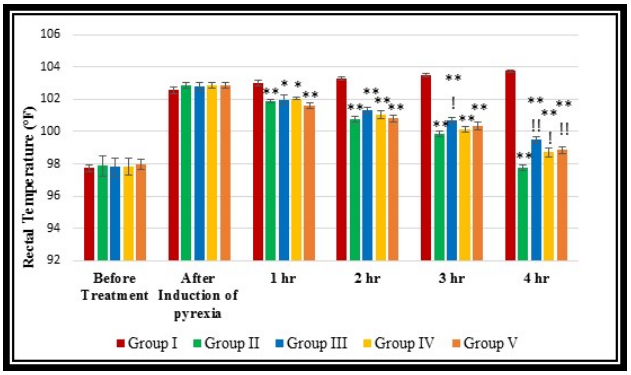

Fig. 3: Antipyretic activity of ethanol extract of *Fragaria ananassa* and *Actinidia deliciosa* by boiled milk induced hyperthermia

Statistical significance at $^{*,!,‡,\#}$ p≤0.05 as significant, $^{**,!!,‡‡,\#\#}$p≤0.01 as highly significant in comparison to control, standard and treated groups of *Fragaria ananassa* and *Actinidia deliciosa* respectively. One-way ANOVA followed by Tukey's test for multiple comparison. Values are presented as mean ± SEM (n=5).

Antipyretic activity

The results illustrated the antipyretic activity of ethanol extract of the *Fragaria ananassa* and *Actinidia deliciosa* and their combination by using boiled milk

induced hyperthermia are presented in table 3. Post hoc Tukey test showed significant decrease in rectal temperature throughout the treatment period by test groups as well as paracetamol (reference standard) in comparison to control group. Whereas there was significant ($p\leq0.05$) decrease in rectal temperature at 3 hours and highly significant ($p\leq0.01$) decrease at 4 hours by EEFA as compared to reference standard. However, significant ($p\leq0.05$) and highly significant ($p\leq0.01$) decrease at 4 hours was observed by EEFA and combination in comparison to reference standard. The percent reduction in pyrexia of test and standard group is reported in fig. 4.

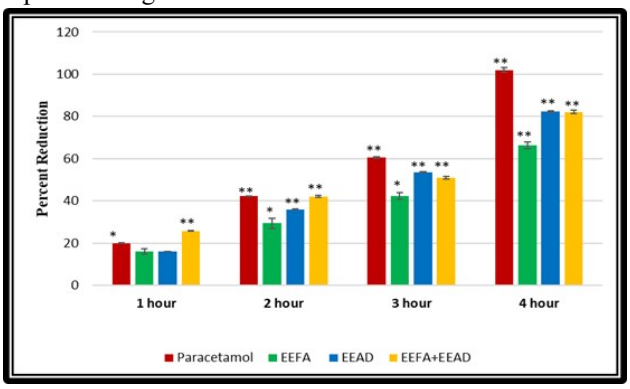

Fig. 4: Percentage inhibition of pyrexia after 1 till 4 hours of dosing with paracetamol (100mg/kg/day), EEFA (800mg/kg/day), EEAD (800mg/kg/day) and EEFA+EEAD (400 + 400mg/kg/day). The data was evaluated by one-way ANOVA. *P≤0.05 and **P≤0.01 are taken as statistically significant from control.

DISCUSSION

This study was conducted to estimate the analgesic, anti-inflammatory and anti-pyretic activity of the ethanol extract of *Fragaria ananassa*, *Actinidia deliciosa* and their combination by using three separate experimental models. The ethanol was selected as an extracting medium to get better yield of phytochemicals as well as for the avoidance of harmful outcomes produced by other organic solvents.

A number of conventional drugs are utilized for the management of inflammation. However, screening of novel anti-inflammatory products with increased efficacy and reduced toxicity is the need of time. Present study revealed the medicinal importance of bioactive compounds present in the strawberry and kiwi fruits extracts. These fruits are widely used for their nutritional benefits but their medicinal values are not clearly understood.

Different methods are used to assess anti-inflammatory response of novel anti-inflammatory compounds however reduction of paw edema in rats initially induced by carrageenan appears to be the best utilized *in-vivo*

Table 1: Anti-inflammatory activity assessment of ethanol extract of *Fragaria ananassa* (EEFA) and *Actinidia deliciosa* (EEAD) and their combination by carrageenan induced paw edema

Group/Treatment	Volume of Paw After Carrageenan injection (cm)					PI after 4 hours
	0 min	1 hour	2 hour	3 hour	4 hour	
GP I (Distilled Water)	2.01±0.12	3.56±0.18	4.26±0.11	5.08±0.15	5.74±0.19	----
GP II (Aspirin 100mg/kg/day)	2.14±0.15	2.76±0.16	2.88±0.17**	2.58±0.12**	2.40±0.11**	93.02%
GP III (EEFA 800mg/kg/day)	2.20±0.10	3.09±0.29	3.69±0.20	4.06±0.42^{a}	3.97±0.37^{**aa}	52.54%
GP IV (EEAD 800mg/kg/day)	2.34±0.12	2.75±0.27	3.11±0.30**	3.26±0.27**	3.11±0.29**	79.35%
GP V EEFA+EEAD (400+400mg/kg/day)	2.67±0.14**	3.25±0.08	3.23±0.26*	3.78±0.31^{*a}	3.34±0.25**	82.03%

n=5$^{*,\dagger,\ddagger,\#}$ p≤0.05 as significant, $^{**,\dagger\dagger,\ddagger\ddagger,\#\#}$p≤0.01 as highly significant against control, standard and treated groups EEFA and EEAD respectively

Table 2: Analgesic activity assessment of ethanol extract of *Fragaria ananassa* (EEFA) and *Actinidia deliciosa* (EEAD) and their combination by hot plate method

Group/Treatment	Reaction time in seconds				
	0 min	15 min	30 min	45 min	60 min
GP I (Distilled water10ml/kg/day)	3.59±0.16	3.59±0.13	3.54±0.14	3.53±0.11	3.53±0.10
GP II (Aspirin 100mg/kg/day)	4.17±0.35	8.05±0.45** (24.51%)	8.62±0.41** (28.11%)	9.05±0.35* (30.82%)	9.32±0.37* (32.53%)
GP III (EEFA 800mg/kg/day)	3.67±0.23	6.59±0.49 (17.88%)	7.99±1.69* (26.45%)	9.44±1.14** (35.33%)	12.20±1.81** (52.23%)
GP IV (EEAD 800mg/kg/day)	4.81±0.57	9.62±0.97** (31.66%)	8.42±1.36** (23.76%)	11.63±1.51** (44.89%)	12.16±1.33** (48.38%)
GP V EEFA+EEAD (400+400mg/kg/day)	5.19±0.81	9.08±1.62** (26.26%)	7.79±0.18* (17.55%)	10.52±1.70** (35.98%)	11.72±1.42** (44.09%)

n=5$^{*,\dagger,\ddagger,\#}$ p≤0.05 as significant, $^{**,\dagger\dagger,\ddagger\ddagger,\#\#}$p≤0.01 as highly significant against control, standard and treated groups EEFA and EEAD respectively.

Table 3: Antipyretic activity assessment of ethanol extract of *Fragaria ananassa* (EEFA) and *Actinidia deliciosa* (EEAD) and their combination by boiled milk induced hyperthermia

Group/Treatment	Rectal Temperature (°F)					
	Before Treatment	After Pyrexia Induction	1 hour	2 hours	3 hour	4 hour
GP I Distilled water (10ml/kg/day)	97.72±0.21	102.56±0.20	102.98±0.17	103.28±0.13	103.48±0.13	103.74±0.08
GP II Paracetamol (100 mg/kg/day)	97.86±0.65	102.88±0.17	101.88±0.13**	100.76±0.19**	99.84±0.17**	97.76±0.17**
GP III EEFA (800mg/kg/day)	97.80±0.58	102.78±0.24	101.98±0.28**	101.32±0.17**	100.68±0.17$^{**!}$	99.48±0.21$^{**!!}$
GP IV EEAD 800mg/kg/day)	97.84±0.53	102.84±0.19	102.04±0.09**	101.04±0.23**	100.16±0.17**	98.72±0.28$^{**!}$
GP V EEFA+EEAD (400+400mg/kg/day)	97.96±0.32	102.86±0.18	101.60±0.20**	100.80±0.22**	100.36±0.24**	98.84±0.19$^{**!!}$

n=5$^{*,!,‡,\#}$ p≤0.05 as significant, $^{**,!!,‡‡,\#\#}$p≤0.01 as highly significant against control, standard and treated groups EEFA and EEAD respectively

technique (Chakraborty *et al.*, 2004, Agarwal *et al.,*2019).The edema of inflammation is primarily associated with polymorpho nuclear leucocytes and kinins in addition to prostaglandins (Damas *et al.*, 1986). Moreover, this edema has developed in two phases starting from serotonin and histamine release in earlier stages whereas prostaglandin release accelerates the process of swelling in later part.

During anti-inflammatory analysis, EEFA+EEAD combination showed highly significant activity against control with percent inhibition of 82.03% at the end of 4th hour against control. EEAD alone got highly significant anti-inflammatory activity with percent inhibition of 79.35% at same time however substantial anti-inflammatory activity was exhibited by EEFA with moderate percent inhibition of 52.54%. A study reported by Clark & Cumby (1975) demonstrated that flavonoids present in different plant parts can inhibit inflammatory prostaglandins. Strawberry and kiwi fruits are also rich in flavonoids that can explain its significant anti-inflammatory effects. The synergistic effect of the combination of EEFA and EEDA also verifies the same.

Analgesics are selectively used to relieve pain by acting on peripheral or central nervous system without altering consciousness. Vogel in 2010 described Hot plate as one of the best methods for assessing the analgesic activity. This method is used for assessing central analgesic activity which is working due to composite supra-spinally integrated behavior (Chapman *et al.,* 1985; Vogel *et al*, 2010) In present study, same method was employed for screening the analgesic activity triggered by thermal stimuli. Our results revealed that both ethanol extract of *Fragaria ananassa*, *Actinidia deliciosa* and their combination showed significant inhibitory effect on pain response in comparison with control group with respect to time.

Maximum analgesic activity was observed with EEFA with 52.23% increase in reaction time at 60 min which is far greater than the standard group reading at same time i.e. 32.53. Likewise EEAD also exhibited substantial analgesic activity with 48.38% increase in reaction time at 60 min against control. Whereas EEFA+EEAD combination exhibit analgesic activity with a maximum of 44.09% increase in reaction time against control group. Previous studies supports that compounds rich in flavonoids showed promising pain killing ability (Sengupta *et al*., 2012; Xiao *et al.*, 2016). Numerous phytochemical studies have revealed the presence of flavonoids in both extracts of *Fragaria ananassa* and *Actinidia deliciosa* fruits that might play significant role in pain reduction against thermal stimuli (Zhang *et al*, 2008; Al-Kawaz &Almashhedy, 2015; Gunduz, 2015; Rafique & Akhtar, 2018).

Fever is one of the common complaints which we encounter in our daily lives. It is an ordinary response that a body creates against any infectious agent, inflammation or tissue damage. Natural products are reflected as safer choice for the management of fever especially in adolescent when compared with available antipyretic drugs which are more toxic and could affect the body organs. In current analysis of anti-pyritic activity, there was significant decrease in rectal temperature at 3rd and highly significant decrease at 4th hour by EEFA against control. Similar pattern were also observed by EEFA and EEFA+EEAD combination in comparison to control.

Antipyretic effects of natural extracts are usually associated with the presence of phenolic compounds and flavonoids (Sindhu *et al.*, 2015). Subsequently, both fruits are known to possess abundant amount of flavonoids as well as phenolic compounds which are working as principle inhibitor of lipoxygenase as well as cyclooxygenase (Zhang *et al*, 2008; Wojdyło *et al.*, 2017). Hence, these extracts might show antipyretic effect by

reducing the prostaglandin biosynthesis in hypothalamus via inhibiting COX-3 enzymes.

These outcomes clearly support that kiwi and strawberry fruit might possess promising role in minimizing the sufferings associated with pain, inflammation and hyperthermia but still more and more preclinical and clinical research are required to establish its true medicinal potential.

CONCLUSION

It has been concluded that Ethanol extract of both *Fragaria ananassa* and *Actinidia deliciosa* and their 1:1 combination contain significant anti-inflammatory, antipyretic and analgesic properties. Although further studies are needed to validate the claims and to confirm the bioactive ingredients responsible for above activities through mechanism based studies. This research however will have paved the way to formulate new medicines in the specified ailments.

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