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Original article

The anti-inflammatory properties of the methanolic extract of *Cucumis melo* Linn. against prostate enlargement in Wistar rats

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ABSTRACT

In different parts of the world, *Cucumis melo* Linn. (*C melo*) is used for its medicinal properties. The present study examined the effects of a methanolic extract of *C melo* Linn. (F1 hybrid, MECM) on benign prostatic hyperplasia in adult male Wistar rats and evaluated its anti-inflammatory activity *in vivo*. MECM treatment reduced prostate weight mildly. Histopathological studies showed that the extract produced a strong protective effect against the development of BPH by testosterone. The MECM also showed protection from testosterone-induced benign prostatic hyperplasia (BPH). MECM was tested against carrageenan-induced inflammation in rats' paws to determine its anti-inflammatory activity. It was shown that MECM had a pronounced effect on the inflammatory response in the late phase, i.e., one hour after carrageenan injection. Prostaglandins and nitric oxide are primarily responsible for this phase indicating that MECM can modify the production and release of prostaglandin and nitric oxide. A novel formulation containing *C melo* may be able to treat the conditions mentioned above.

1. Introduction

Plants with medicinal properties are quite diverse. There have been approximately 70,000 plant species used for medicinal purposes, ranging from algae to trees (Giannenas et al., 2020; Negi et al., 2018; Van Wyk and Prinsloo, 2018). The tissues of those plants contain certain ingredients, which make them medicinally active (Li et al., 2020; Babich et al., 2020; Galanakis et al., 2020). The ingredients themselves are used as therapeutic agents or as active ingredients in formulations rich in bioactive compounds (Silva et al., 2021; de Amorim et al., 2020). The substance can also be used as a raw material for the manufacturing of drugs under chemical modification (Standau et al., 2019; Schmid et al., 2018; Singh et al., 2018).

The abnormal enlargement of the prostate gland is called benign prostate hyperplasia (BPH). This condition is also known as benign prostate enlargement (BPE), adeno fibro myomatous hyperplasia, or benign prostatic hypertrophy (Wang et al., 2018; Jin et al., 2019; El-Sherbiny et al., 2021). When the prostate is enlarged, the urethra may be compressed, resulting in a slight to severe obstruction of urine flow (Dmochowski, 2005; Calogero et al., 2019). Although the cause of this disease is unknown, obesity and lack of exercise predispose the condition (Sones et al., 2021; Cunto et al., 2019). In severe cases, there will be pain or burning when urinating and loss of control of the bladder, and sometimes hematuria (Neuzillet et al., 2017). As men age, enzymes such as aromatase and 5-alpha reductase increase in activity (Martin and Touaibia, 2020). These enzymes aid in the conversion of androgen hormones to oestrogenic and dihydrotestosterone (DHT), respectively (Detering et al., 2017; Mohamad et al., 2018). As a result, the levels of testosterone decrease, while the levels of oestrogen

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and DHT increase (Benrick et al., 2017; Li et al., 2018). BPH results in hyperplasia of both glandular epithelial cells and stromal cells (including muscle fibres) (Liu et al., 2021; Nian et al., 2021; Chiang et al., 2019). However, out of the two tissues, stromal hyperplasia is more prevalent (Sterling et al., 2019).

For several years, BPH was only treated by surgery (Parvathaneni et al., 2019). A variety of new methods are available nowadays to decrease the size of enlarged prostates (Le et al., 2020). The prostate gland is a mixture of capsular tissue and stromal tissue, with a high concentration of androgen receptors (Kato et al., 2021). These receptors and oestrogen can be used to target drug therapy (Yu et al., 2020). Since the bladder has few alpha receptors (6), we can block them selectively without affecting bladder contractions (Thomas et al., 2017; Zhang et al., 2020). Also, herbal medicines can be used for the treatment of cancerous tumours (Kuo et al., 2019). Better treatment of BPH may be developed with fewer side effects through further research in this area (Barakat et al., 2020). There are several herbal remedies commonly used around the world, and in the United States, saw palmetto extract obtained from *Sereno arepens* is the most commonly used drug (Ruan et al., 2021).

By disrupting the internal environment of the body, inflammation occurs, either local or systemic. This condition may be caused by a variety of stimuli (Salvador et al., 2021). Mechanical trauma or injury, infections by pathogenic organisms, toxins, and ischemia are a few of the causes for inlammation (Furman et al., 2019). The pathogenesis of certain diseases, such as diabetes, cancer, and asthma, may be linked to inflammation, suggesting that inflammation is a factor for these diseases (Ferrucci and Fabbri, 2018; Hartman et al., 2019).

Like other members of the *Cucurbitaceae* family, muskmelon and cantaloupe are part of the family *Cucurbitaceae* (Rajasree et al., 2021). This plant, which belongs to the family *Cucurbitaceae*, contains bioactive compounds that can treat various ailments (Prakash et al., 2021). The methanolic extract of the seeds contains phenolic compounds, particularly flavonoids, which makes it particularly effective in treating various ailments. Cantaloupe leaf and stem extracts exhibit significant antioxidant activity (Winter et al., 1962). The current study examined the anti-inflammatory effects of methanolic extract of *Cucumis melo in vivo*. Additionally, its additive or synergistic effects were evaluated when it was combined with standard anti-inflammatory drugs.

2. Materials and methods

The material used for the study was fruits of *Cucumis melo* Linn. (Family: *Cucurbitaceae*) purchased from Vadanerkunam, Tindivanam T.K, Villupuram Dt, Tamilnadu and identified and authenticated by experts of the Department of Botany, St. Berchmans College, Changanacherry, Kottayam.

2.1. Preparation of fruits for extraction

The fruits of *C. melo* were cut into pieces with a stainless-steel knife. Approximately 100 g (including the seeds), and the pieces of fruit and seeds were dried at 60 °C. After the dried fruits were comminuted, they were passed through a no. 10 sieve and used for extraction.

2.2. Preparation of the extract

The coarse powder prepared from the fruits and seeds was extracted with methanol (absolute) by a hot continuous percolation process. Fractions of 100 g of the dry powder were packed in filter paper thimbles and extracted with a Soxhlet extractor five times per day for three consecutive days. The marc was then further extracted with 95 % methanol till the extractive became almost colourless. The process of extraction was repeated with and the entire alcoholic extractives were combined, and most of the solvent was recovered by distillation under reduced pressure (Prakash et al., 2021).

After combining the extracts, they were evaporated under a vacuum to form a soft extract. After weighing, reheating, and weighing again, the final extract was assured to be alcohol-free. After storage in a vacuum desiccator over silica gel, the extract was used to conduct further studies.

2.3. Animals

The animals used for the current study were obtained from the small animals breeding station, Kerala Veterinary and Animal Sciences University, Mannuthy, Thrissur. The animals were maintained under the standard animal house conditions like housing facilities, bedding materials, temperature, light and humidity conditions, noise-free atmosphere, feed, drinking water facilities, and sanitation.

2.4. Protective effect of MECM on BPH

The protective effect of MECM in BPH was evaluated on adult male, healthy, Wistar rats 150–200 g in weight. The experimental design is illustrated in Table 1. Adequate drinking water was given throughout the experiment. Animals were grouped into six. Group I served as the negative control. Normal saline was given to the control group of six animals for 1–28 days. Group II served as the positive control. Normal saline was given for the first 14 days. Between 15 and 28 days, testosterone propionate 7 $mgkg^{-1}$ was administered. Group III was the standard and they were treated with normal saline for the first 14 days. Testosterone propionate 7 $mgkg^{-1}$ and flutamide 30 $mgkg^{-1}$ was given for 15–28 days. Flutamide served as the standard. Group IV rats were treated with MECM 200 $mgkg^{-1}$ body weight for 28 days. Testosterone propionate 7 $mgkg^{-1}$ in corn oil was given from 15 to 28 day along with MECM. The group V rats were treated with MECM 400 $mgkg^{-1}$ bodyweight for 28 days. Testosterone 7$mgkg^{-1}$ in corn oil was given from 15 to 28 days. The group VI rats were treated with MECM 200 $mgkg^{-1}$ bodyweight for 28 days. 15 $mgkg^{-1}$ flutamide and 7 $mgkg^{-1}$ testosterone in corn oil were given along with MECM from 15 to 28 days. The prostate gland was dissected and weighed. Histopathological studies were carried out using H&E staining.(See Table 3.).

2.5. Anti-inflammatory activity in vivo

Albino rats of both sexes having 150–200 g weight was used to conduct the study. The rats were segregated into 5 groups (n = 6) as given in Table 2. (Group **I:** control group and received vehicle 0.5 % w/v of CMC (2 mL orally); Group II: standard indomethacin at a dose of 10 mg kg^{-1} $bodyweight^{-1}$ orally as a 2 mL suspension in 0.5 % w/v of CMC; Group III: low dose MECM 200 mg kg^{-1} $bodyweight^{-1}$ orally as a 2 mL suspension in 0.5 % w/v of CMC; Group IV: high dose MECM 400 mg kg^{-1} $bodyweight^{-1}$ orally as a 2 mL suspension in 0.5 % w/v of CMC; Group V: received MECM 200 mg kg^{-1} $bodyweight^{-1}$ + Indomethacin 5 mg kg^{-1} $bodyweight^{-1}$).

The assay procedure was carried out as described by Winter et al (Winter et al., 1962) (Nascimento-Gonçalves et al., 2018). Paw edema was induced in rats by injecting 0.1 mL of 1 % solution of carrageenan in the plantar tissue of the left hind paw. An anti-inflammatory activity study was conducted using a plethysmograph apparatus, which measures the paw volume. The right paw

Table 1
A study design to evaluate the protective effects of MECM on benign prostatic hyperplasia (BPH).

Group No.	Group name	Days (0–14)	Days (15–28)	Route
I	Control	Normal saline	Normal saline	p.o
II	Positive Control	Normal saline	Testosterone-7 mg kg^{-1} $bodyweight^{-1}$	I.M
III	Standard	Normal saline	Testosterone-7 mg kg^{-1} $bodyweight^{-1}$ + Flutamide-30 mg $kg^{-1}$$bodyweight^{-1}$	Testosterone-IM Flutamide-p.o
IV	Low dose	MECM 200 mg kg^{-1} $bodyweight^{-1}$	MECM-200 7 mg kg^{-1} $bodyweight^{-1}$ + Testosterone-77 mg kg^{-1} $bodyweight^{-1}$	MECM-p.o TTestosterone-IM
V	High dose	MECM 400 mg kg^{-1} $bodyweight^{-1}$	MECM-400 7 mg kg^{-1} $bodyweight^{-1}$ + Testosterone-7 mg kg^{-1} $bodyweight^{-1}$	MECM-p.o Testosterone-IM
VI	Combination	MECM 200 mg kg^{-1} $bodyweight^{-1}$	MECM-200 mg kg^{-1} $bodyweight^{-1}$ + Testosterone-7 mg kg^{-1} $bodyweight^{-1}$ + Flutamide-15 mg kg^{-1} $bodyweight^{-1}$	M ECM-p.o Testosterone-IM Flutamide-p.o

Table 2
A design for evaluating the anti-inflammatory activity.

Group	Group	Drugs given	Route
I	Control (A)	05 % w/v of CMC (2 mL)	P.O
II	Standard (B)	Indomethacin-10 mg kg^{-1} $bodyweight^{-1}$	P.O
III	Low dose	MECM-200 mg kg^{-1} $bodyweight^{-1}$	P.O
IV	High dose	MECM-400 mg kg^{-1} $bodyweight^{-1}$	P.O
V	Combination	MECM-200 mg kg^{-1} $bodyweight^{-1}$ + Indomethacin 5 mg kg^{-1} $bodyweight^{-1}$	P.O

acted as a reference to the non-inflamed paw for comparison. The increase in the paw volume was measured every hour by using a plethysmograph in control, standard and test groups, up to 4 h after the carrageenan injection. A percentage of the increase in paw volume was calculated. The increase in the paw volume in animals administered with standard drug and all the test groups were compared with the increase in paw volume of control animals, at every hour, up to 4th h. The percentage of inhibition of edema in volume was calculated using the formula (Al-Trad et al., 2019).

$$\%\ inhibition\ =\ (1 - V_t/V_c)\ X100$$

Where V_t is the relative change in the test and V_c is that of the control.

The statistical analysis was performed using SPSS 17. We also used one-way ANOVA for comparisons between groups and Dunnett's multiple comparisons for pair-wise comparisons of means if the analysis of variance was significant. We considered $P < 0.05$ to be statistically significant.

3. Result

3.1. Effect of MECM on prostatic hypertrophy

A mild reduction of prostate weight was observed on MECM treatment. However, it did not show any statistically significant reductions in prostate weight compared to the positive control group. At the same time histopathological studies showed that the extract produced a strong protective effect against the development of BPH by testosterone (Fig. 1). Results of all test groups were comparable with the standard drug and the combination produced synergistic activity (Fig. 2).

3.2. Anti-inflammatory activity of MECM

After sub-plantar injection with carrageenan, swelling and an increase in paw volume occurred in animals of the control, test, and standard groups. At 3rd h, the percentage inhibition of edema by the standard group (indomethacin-treated) animals was 62.1 ± 1.28, which was statistically significant (Fig. 3).(See Fig. 4.).

Table 3
The reduction in paw volume expressed as inhibition of edema after administartion of methanolic extract of *Cucumis melo* Linn. (MECM) in Wistar rats.

No	Group	% inhibition of edema (Mean ± SEM) at various times after drug treatment			Groups compared and significance
		3 Hour (I)	4 Hours (II)	6 Hours (II)	
1	Control (A)	00.00	00.00	00.00	
2.	Standard (B)	62.1 ± 1.28	63.5 ± 0.281	63.7 ± 1.11	AI & BI, *** AI & BII*** AI & BIII***
3.	MECM (200 $mgkg^{-1}$) (C)	12.7 ± 1.07	13.8 ± 1.113	15.6 ± 1.0	AI & CI*** AI & CII *** AI & CIII *** BI & CI ***
4.	MECM (400 $mgkg^{-1}$) (D)	24.1 ± 2.05	24.1 ± 2.05	26.7 ± 1.0	AI & DI *** AI & DII *** AI&DIII *** DI & BI *** DI & CI ***
5.	Std + MECM(E)(200 $mgkg^{-1}$)	43.4 ± 1.75	43.4 ± 1.75	47 ± 2.31	AI & EI *** AI & EII*** AI & EIII *** EI & CI *** EI & DI ***

* Significant, $P < 0.001$, ANOVA with Dunnett's multiple comparison, $F = 325$, $N = 6$.

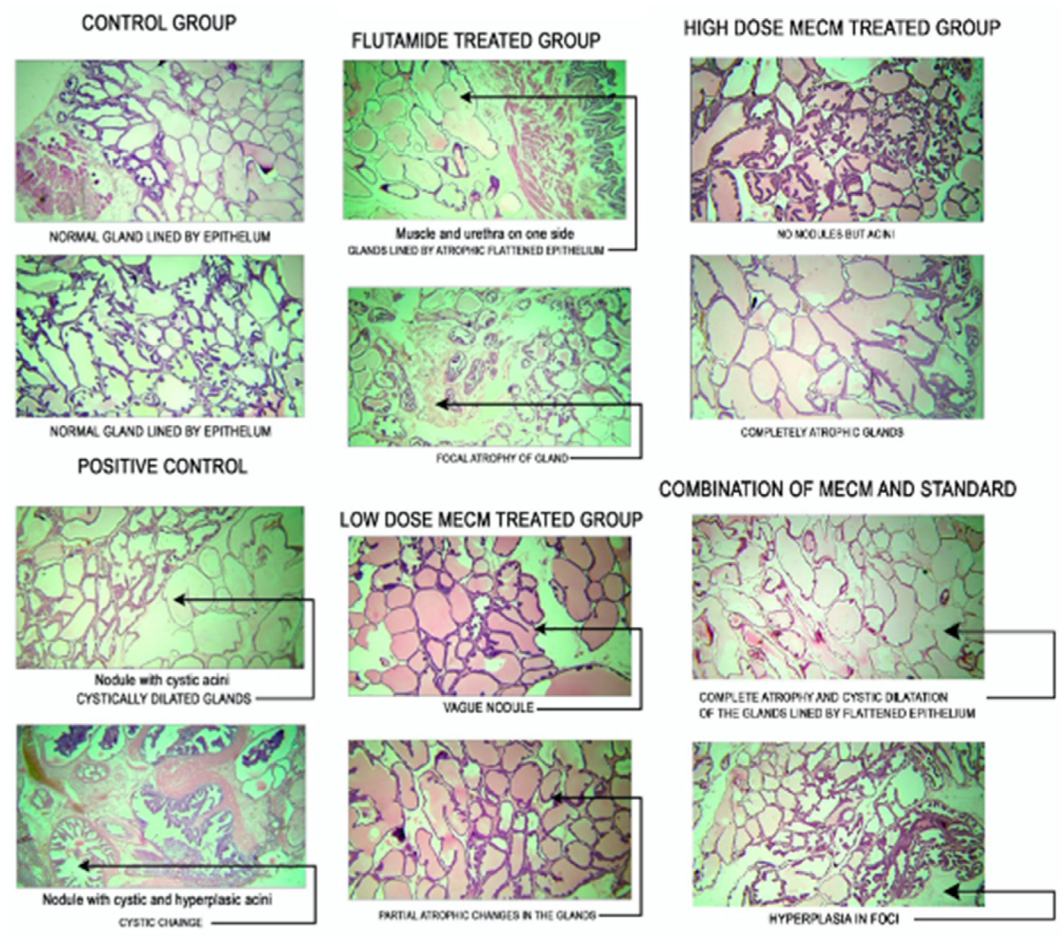

Fig. 1. Histopathological studies showing protective effect of methanolic extract of *Cucumis melo* Linn. (MECM) against the development of benign prostatic hyperplasia (BPH) by testosterone in Wistar rats.

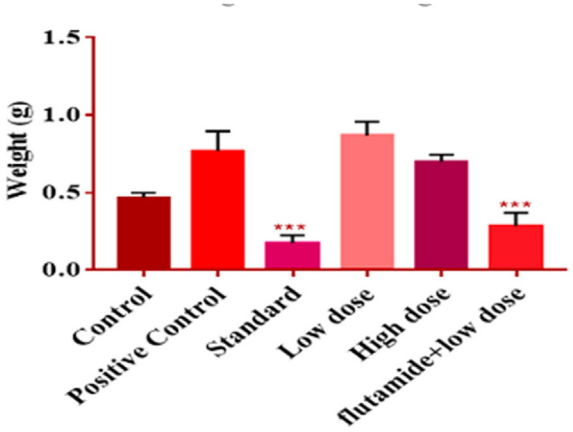

Fig. 2. Effect of Methanolic extract of *Cucumis melo* Linn. (MECM) on prostatic hypertrophy in Wistar rats.

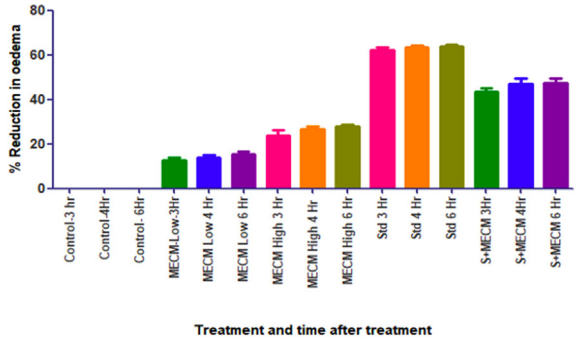

Fig. 3. Percentage reduction in paw edema at 3rd, 4th, and 6th h after administration of methanolic extract of *Cucumis melo* Linn. (MECM) in Wistar rats.

For animals that were treated with MECM low dose (200 $mgkg^{-1}$), the percentage inhibition of edema was 12.7 ± 1.07, with MECM high dose (400 $mgkg^{-1}$) it was 24.1 ± 2.05, which was significantly different from the control group. The percentage inhibition of edema in animals on combination therapy was 43.4 ± 1.75. The reduction in paw volume expressed as inhibition in all three test groups were statistically significant ($p < 0.01$) when compared with the control group.

4. Discussion

It is challenging to assess nodule formation in rat prostate (Nascimento-Gonçalves et al., 2018; Al-Trad et al., 2019; Palmieri et al., 2019). However, the number of papillae and amount of secretion can assess the cystic change/hyperplasia in the epithelium (De Nunzio et al., 2020). The prostate shows glandular and stromal components, and the glands are lined by tall columnar mucinous epithelium. The glands became less in number and lining epithelium became flattened in the standard drug-treated group. Hyperplasia of prostatic epithelial cells and stromal cells occurs, which

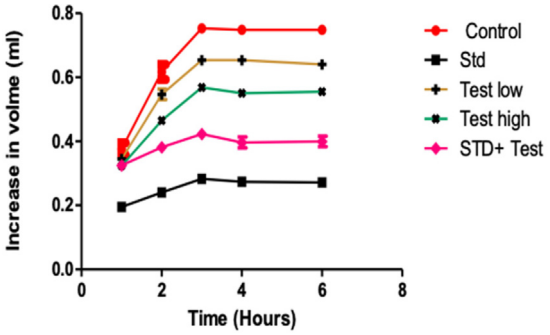

Fig. 4. Increase in paw volume in mice over time in response to treatment with methanolic extract of *Cucumis melo* Linn. (MECM) in Wistar rats.

subsequently results in lower urinary tract symptoms (Jin et al., 2021; Zhang et al., 2021; Siddiqui et al., 2021).

The prostate gland of BPH-induced animals displayed an increase in the weight of prostate gland. A reduction in the weight of prostate gland indicates protective effect. A mild reduction of prostate weight was observed on MECM treatment, but did not show any statistically significant reductions in the prostate weight compared to the positive control group.

Glands of positive control group showed typical signs of hyperplasia. Flutamide treated group showed focal atrophy of glands and lining became flat. So this is a clear indication of the effect of standard drugs. In low dose (200 $mgkg^{-1}$) there were partial atrophic changes which show its action against hormone-induced hyperplasia. In high-dose treatment group (400 $mgkg^{-1}$) the glands were completely atrophic and it gave better result than low dose treated group. This proves that the extract produced increased activity in a dose-dependent manner. Combination therapy (5 $mgkg^{-1}$ Flutamide with 200 $mgkg^{-1}$ MECM) showed complete atrophy and cystic dilatation of the gland lined by flattened epithelium. Here the dose of the standard drug was reduced in half and it was given with low dose test.

Previous studies using *in vitro* models have confirmed that MECM is capable of preventing protein denaturation, stabilizing the membranes and inhibiting protease activity (Prakash et al., 2021). Several factors contribute to the development of edema, including histamine, bradykinin, and serotonin (Rukshala et al., 2021). A biphasic impact is observed in rat paw edema induced by carrageenan (Jisha et al., 2019). As a result of the release of histamine or serotonin, the first phase occurs, and the second phase occurs due to the release of bradykinin, protease, and prostaglandin (Nantel et al., 1999). Approximately-one hour after carrageenan injection, COX-2 expression reaches a maximum (Portanova et al., 1996). Portanova et al (Portanova et al., 1996) for example, have described how various pathological processes underlying inflammation interact with various mediators, including prostanoids (Li et al., 2020). In carrageenan-induced paw edema, endothelial and inducible nitric oxide synthases (eNOS and iNOS) also contribute to edema (Bostanci et al., 2013). Edema caused by carrageenan is first triggered by biological amines such as histamine (Kruslin et al., 2017). In the present study, the anti-inflammatory activity of MECM in acute inflammation was evaluated with a carrageenan-induced rat model. When injected in to the plantar surface of rats, certain chemicals, such as formaldehyde, carrageenan, histamine, and serotonin, can cause an inflammatory response. In animal models, acute inflammation is commonly induced using these chemicals. In the present study, it was shown that MECM had a pronounced effect on the inflammatory response in the late phase, i.e., one hour after carrageenan injection. Prostaglandins and nitric oxide are primarily responsible for this phase (Ferrante et al., 2020) indicating that MECM can modify the production and release of prostaglandin and nitric oxide [60].

5. Conclusions

Inflammation in the prostate is still a subject of debate; however, it is likely to be complex. As a result of an ongoing wound healing process, hyperproliferative programs trigger the development of BPH nodules. Prostate inflammation leads to an accumulation of immune-competent cells, primarily T lymphocytes, and macrophages. In the present study, we evaluated the protective effect of MECM on BPH using *in vivo* models and found that its anti-inflammatory activity was significant. From the results presented in this study, it is evident that muskmelon fruits may contain one or more natural phytochemicals with medicinal value.

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7. Institutional review board statement

The Institutional Animal Ethics Committee approved the experimental protocols followed for Professional and Advanced Study (CPAS, Department of Pharmaceutical Sciences Cheruvandoor-Ettumanoor), as per order No. IAEC/PHD/DPS/2018–01 dated 10–01-2018.

CRediT authorship contribution statement

R.S. Rajasree: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Funding acquisition. **Sibi P. Ittiyavirah:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Punnoth Poonkuzhi Naseef:** Data curation, Writing – review & editing, Funding acquisition. **Mohamed Saheer Kuruniyan:** Writing – review & editing, Funding acquisition. **Muhammed Elayadeth-Meethal:** Data curation, Writing – review & editing, Funding acquisition. **S Sankar:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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