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Original research

Development and evaluation of antiobesity polyherbal granules: A full spectrum weight management concept

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ABSTRACT

Background: To improve the therapeutic efficacy of herbs, the "Ayurveda literature- *Sarangdhar Samhita*" emphasized on the concept of polyherbalism. Ready to drink granules of different ayurvedic herbs that are targeting all possible mechanisms responsible to cure obesity were prepared and evaluated for their preclinical therapeutic efficacy in high-fat-diet-(HFD) induced obese rats.

Methods: Rats were fed an HFD (58 E% as fat) or a standard diet and administered granules (0.1 and 0.3 g/kg) for 42 days. The body weight and food intake of rats were determined weekly whereas the plasma total cholesterol (TC), glucose and triglyceride (TG) levels and organ (adipose tissue and liver) weight measured at the end of the experiment.

Results: The result found that body and adipose tissue weight and plasma TC and TG levels were significantly lowered in 0.3 g/kg granules treated group in comparison to the HFD control group.

Conclusion: The results support the traditional weight-reducing effect of the plant extracts. The combination of plant extracts demonstrated excellent weight and fat reducing effect provided rationale for usage and generates conviction among users as effective formulae for weight management and holds the potential to treat obesity.

1. Introduction

Overweightness is one of the most prevalent health issues in developing and developed countries and a risk factor for non-communicable diseases (Bhurosy and Jeewon, 2014; Hruby and Hu, 2015). The preferred non-pharmacological treatment for obesity is dieting and physical exercise (Kelley et al., 2016). However, due to the hard and sedentary routine, it becomes difficult to exercise in a regular manner. Currently, available drugs for obesity treatment are centrally acting and have severe cardiac side effects (Marrelli et al., 2016). Alternatively, medicinal plant-based supplements are being generally used to manage chronic disorders like obesity, diabetes etc, due to very fewer side effects and cost-effective compared to chemically synthesized drugs (Chandrasekaran et al., 2012).

Possible approaches for obesity treatment are a decrease in calorie intake, reduction in fat absorption, an increase of energy expenditure, decrease preadipocytes differentiation, decrease lipogenesis and increase lipolysis (Mohamed et al., 2014). The major problem in obesity treatment is that if the individual mechanism is targeted than the body's homeostasis will equilibrate the condition and drug may not give a proper impact. For example, if appetite suppressant is given than body homeostasis will decrease energy expenditure or through else, try to maintain metabolic equilibrium, because of this majority of drugs are ineffective for treatment.

To improve the therapeutic efficacy of herbs, the *Ayurvedic* literature *Sarangdhar Samhita*' emphasized on the concept of polyherbalism (Dev et al., 2019; Karole et al., 2020; Parasuraman et al., 2014; Shan et al., 2020). The desired therapeutic effect of plants can be achieved by combining the multiple plants in a specific proportion (Parasuraman et al., 2014). So, plants having the possible mechanism and potential to treat obesity were selected for full spectrum weight management formula. In this study, we formulate ready to drink granules of different ayurvedic herbs that are targeting all possible mechanisms responsible to cure obesity. List formulae of selected herbs and their potential antiobesity targets mentioned in Table 1. An anti-obesity effect of a polyherbal granule (PHG) in HFD-induced rats was investigated in this research. The scientific evaluation provided rationale for usage and generates conviction among users as effective for weight management.

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2. Material and methods

2.1. Identification and procurement of plant extract

The potential antiobesity herbs extract such as ethanolic extract of *Achates aspera* leaves, an aqueous extract of *Camellia sinensis* leaves, an aqueous extract of *Salacia reticulate* roots, an aqueous extract of *Vitis Vinifera* seeds, an aqueous extract of *Phaseolus vulgaris* seeds were selected and procured from Sunpure extracts Pvt. Ltd. L-99A, Dilshad Garden, Delhi-110095, India.

2.2. Formulation and evaluation of polyherbal granules

2.2.1. Preformulation parameters

The solubility of each plant extract was checked by dissolving in water. It was found that all the plants extract is soluble in water except *Achyranthes aspera*, which is sparingly dissolved in water. For enhancing the solubility of the *Achyranthes aspera* extract powder, tween 80 was used as a surface-active agent. Flow properties of individual plant extract were evaluated by "bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose" as per standard method.[8]

2.2.2. Preparation of the polyherbal mixture

Accurately weight ethanolic extract of *Achyranthes aspera* leaves (50.13%), aqueous extract of *Camellia sinensis* leaves (24.79%), aqueous extract of *Salacia reticulate* roots (5.57%), aqueous extract of *Vitis Vinifera* seeds (16.71%) and aqueous extract of *Phaseolus vulgaris* seeds (2.75%), were triturated in dry motor pastel and passed through 75 μm sieve to obtain a homogenized polyherbal mixture.

2.2.3. Formulation of polyherbal granules

Granules were formulated by a wet granulation technique. Initially, plant mixture and citric acid were mixed, followed by sucralose, starch and Dicalcium phosphate were added. Distilled water was used to form a lumpy mass, passed through sieve no. 20 and granules were dried in the oven at temperature 25°c for 15 min. Magnesium stearate was added at the end.

2.2.4. Evaluation of granules

The organoleptic properties and flow properties of herbal granules were evaluated. For organoleptic evaluation, a five-point hedonic rating scale was used for rating the attributes, viz., colour, taste, flavour and overall acceptability. For the same 10 trained panellists were selected based on their sensitivity to different tastes and evaluation was carried out (Amerine et al., 1965). Flow properties parameters like "bulk density, tap density, Carr's index, Hausner's ratio and angle of repose" were obtained for the polyherbal granules (Petchi et al., 2014).

2.3. Evaluation of the antiobesity potential of PHG in HFD induced obese rats

2.3.1. Animal experiments

Wistar rats weighing between 150 and 250 g m of either sex were acquired from Jai Research Foundation, Vapi, Gujarat and housed in standard cages by maintaining a temperature of 22 ± 2 °C. All investigational procedures were approved by the Institutional Animal Ethics Committee (approval no. SSR/IAEC/2018/02).

After seven days of acclimatization, female rats were divided into five groups (n = 6):

Group A (lean 6 rats) were fed with a standard pelleted diet which provided carbohydrates 64.41 E %, protein 22.46 E % and fat 12.61 E%.

Remaining four groups (24 rats) were fed with an HFD providing carbohydrates 26.08 E %, protein 15.69 E % and fat 58.23 E% for 8 weeks. The HFD was prepared as a modification of West et al. (1995)[10] (Refer Table 2).

Group B was fed with HFD for 8 weeks and administered 1 ml/kg of distilled water, p. o/day, for 6 weeks. Group C was fed with HFD for 8 weeks and administered 0.1 g/kg oral gavage of PHG, p. o/day, for 6 weeks.

Group D was fed with HFD for 8 weeks and administered 0.3 g/kg oral gavage of PHG, p. o/day, for 6 weeks.

Group E was fed with HFD for 8 weeks and administered oral gavage of experimental positive control drug- Sibutramine.

At the end of the experiment, the rats were sacrificed, organ and white adipose tissue and brown adipose tissue (BAT) were removed and weighed.

2.3.2. Food and water intake and body weight measurement

Throughout the experimentation food and water intake of rats were measured. The food and water intake was measured in the unit of g/day/rat and ml/day/rat respectively. During the experiment body weight of rats was determined by digital weighing balance (weekly).

2.3.3. Biochemical parameters

At the end of the protocol, TC, glucose and TG levels in plasma were determined using biochemical kits (TC by one-step method, glucose by

Table 2
Composition of the experimental diets.

Ingredients	Standard diet (g/100 g m diet)	High fat diet (g/100 diet)
Casein	20	20
dl-Methionine	0.3	0.3
Corn starch	50	26
Sucrose	15	11
Cellulose	5	5
Corn oil	5	33
Mineral mixture [b]	3.5	3.5
Vitamin mixture [a]	1	1
Choline Bitartrate	0.2	0.2
l-cystein	0.4	0.4

[a] Vitamin Mix for AIN- 76A Rodent Diet (mix. gm/kg) Vitamin A Palmitate 0.8, Vitamin D3 1, Vitamin E Acetate 10, Menadione Sodium Bisulfite 0.08, Biotin, 1.0% 2, Cyanocobalamin, 0.1% 1, Folic Acid 0.2, Nicotinic Acid 3, Calcium Pantothenate 1.6, Pyridoxine-HCl0.7 Riboflavin 0.6 Thiamin HCl0.6 Sucrose 978.42.

[b] Mineral Mix for AIN- 76A Rodent Diet (mix. gm/kg) Sodium Chloride 259 Magnesium Oxide, Heavy, DC USP 41.9, Magnesium Sulfate, Heptahydrate 257.6 Ammonium MolybdateTetrahydrate0.3 Chromium Potassium Sulfate 1.925 Copper Carbonate 1.05 Ferric Citrate 21 Manganese Carbonate Hydrate 12.25 Potassium Iodate 0.035 Sodium Fluoride 0.2 Sodium Selenite 0.035 Zinc Carbonate 5.6 Sucrose 399.105.

Table 1
Description of herbal plants extracts.

Target	Name of plant extract	Part	Family	quantity	Reference
Appetite suppressant	Ethanolic extract of *Achyranthes aspera*	Leaves	*Amaranthaceae*	50.13%	Rani et al. (2012)
Alpha-Amylase inhibitors	Aqueous extract of *Phaseolus vulgaris*	Seeds	*Papilionaceae*	24.79%	Udani et al. (2018)
Adipogenesis inhibitors	Aqueous extract of *Vitis vinifera*	Seeds	*Vitaceae*	5.57%	Zhang et al. (2019)
Energy expenditure And pancreatic lipase inhibitors	Aqueous extract of *Camellia sinensis*	Leaves	*Theaceae*	16.71%	Kim et al. (2011)
Alpha-glucosidase inhibitors	Aqueous extract of *Salacia reticulata*	Roots	*Celastraceae/Hippocrateaceae*	2.75%	Oe and Ozaki (2008)

GOD-POD end-point assay and TG by GPO-PAP end-point method).

2.4. Statistical analysis

All of the results were reported in the form of 'mean ± standard deviation'. The Statistical analysis was done through one-way ANOVA followed by Dunnett's test. The significance level was taken as ($P < 0.05$).

3. Results

3.1. Appraisal parameters of polyherbal granules

The estimated solubility and flow property of the extracts is depicted in Table 3. All the extracts were highly soluble in water and had good flow property except *Achyranthes aspera* extract. The results of the organoleptic evaluation of the PHG exhibited overall acceptability (data are not shown). The results of the flow properties of PHG are shown in Table 4. The data indicate granules have good flow properties.

3.2. Effect of PHG on food intake and water intake

The HFD induced control rats exhibited a cumulative increase in food intake compared with the Group A rats ($P > 0.05$). No significant difference in food intake and water intake was observed during the 6 weeks of oral gavage of 0.1 and 0.3 g/kg of PHG compared to that of the HFD induced control groups (data not shown). Whereas, sibutramine reduced food intake in treatment groups.

3.3. Effect of PHG on body and organ weight

The effects of PHG on body weight gain, white adipose tissue and adiposity index on the groups under study are given in Table 5. The HFD induced control rats exhibited a significant rise in body weight, liver weight, WAT (subcutaneous, periovarian, and peritoneal adipose tissues), BAT and adiposity index compared with the Group A rats ($P < 0.001$). Treatment with 0.1 and 0.3 g/kg of PHG for 6 weeks and sibutramine led to the significant decrease in body weight, liver weight, WAT, BAT and adiposity index as compared to HFD-induced control group.

Table 3
Evaluation of flow property and solubility of plants extract.

Drug	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Angle of repose (°)	Solubility
Ethanolic extract of *Achyranthes aspera*	0.795	0.833	4.56	17.38	Sparingly soluble
Aqueous extract of *Phaseolus vulgaris*	0.312	0.459	32.02	14.99	Highly soluble
Aqueous extract of *Vitis vinifera*	0.526	0.769	31.59	19.13	Highly soluble
Aqueous extract of *Camellia sinensis*	0.4	0.55	27.27	24.22	Highly soluble
Aqueous extract of *Salacia reticulata*	0.5	0.66	24.24	23.11	Highly soluble

Table 4
Evaluation parameters of polyherbal granules.

Sr. No.	Parameter	Value
1	Bulk density	0.625 g m/ml
2	Tapped density	0.667 g m/ml
3	Carr's index	6.296%
4	Hausner's ratio	1.067
5	Angle of repose	26.56°

Table 5
Effect of PHG on body weight gain and adipose tissue.

Parameter	Normal Control	HFD control	HFD +0.1 g/kg PHG	HFD +0.3 g/kg PHG	HFD + Sibutramine
Bodyweight on 8th week (g)	180.31 ± 7.78	195.58 ± 7.46^{a***}	192.51 ± 4.31^{b***}	210.55 ± 5.26^{b***}	217.29 ± 5.57^{b***}
Bodyweight on 14th week (g)	261.33 ± 7.73	320.90 ± 17.87^{a***}	261.12 ± 14.53^{b*}	255.82 ± 15.05^{b***}	259.01 ± 15.23^{b***}
Body weight gain (g)	81.02 ± 0.24	125.32 ± 0.61^{a***}	68.61 ± 0.31^{b***}	45.27 ± 0.31^{b***}	41.72 ± 0.29^{b***}
Liver weight (g)	10.44 ± 0.53	17.57 ± 0.57^{a***}	14.08 ± 2.04^{b**}	12.06 ± 0.97^{b***}	11.406 ± 0.82^{b***}
Peri-ovarian WAT(g)	6.29 ± 1.13	15.001 ± 2.05^{a***}	11.2 ± 1.04^{b**}	9.07 ± 0.58^{b***}	7.88 ± 0.53^{b***}
Peri-renal WAT (g)	7.69 ± 0.802	20.04 ± 0.47^{a***}	15.32 ± 0.47^{b**}	11 ± 0.57^{b***}	9.55 ± 9.91^{b***}
Mesenteric WAT (g)	6.04 ± 0.33	11.105 ± 0.62^{a***}	9.09 ± 0.61^{b*}	7.14 ± 0.77^{b***}	6.57 ± 0.51^{b***}
Whole WAT (g)	20.02 ± 3.33	46.15 ± 5.23^{a***}	35.61 ± 2.38^{b***}	27.21 ± 2.83^{b***}	24 ± 3.86^{b***}
BAT	2.006 ± 0.26	7.003 ± 0.8^{a***}	6.29 ± 0.37^{b***}	4.39 ± 0.37^{b***}	3.44 ± 0.37^{b***}
Adiposity index	03.91 ± 0.47	8.60 ± 0.61^{a***}	4.81 ± 0.48^{b***}	4.24 ± 0.57^{b***}	4.05 ± 0.65^{b***}

The Values are expressed as mean ± SD (n = 6), "a" HFD Control significant compared to Norma Control whereas "b" PHG and Sibutramine treated compared to HFD control group. ***p < 0.001, **p < 0.01 *p<0.05 ^{ns} p>0.05.

3.4. Effect of PHG on biochemical parameters

The efficacy of PHG on the percentage change in plasma TG, glucose and TC level is shown in Fig. 1, Fig. 2 and Fig. 3 respectively. In comparison to HFD induced rats with healthy rats (Normal control) indicated a significant rise in TG, TC and glucose level. However, treatment with a dose of 0.1 and 0.3 g/kg PHG reduced the TG, TC and glucose level in comparison to the group without treatment (Fig. 1). It was found that Sibutramine also reduced TG and TC level in treatment groups.

4. Discussion

Bariatric surgery is the most efficacious for the management of obesity. However, due to its side effects, this surgery is reserved for morbidly obese patients (Wolfe et al., 2016). Physicians often manage overweight and obese patients by counselling and lifestyle modification programs (Durrer Schutz et al., 2019). Nevertheless, the efficacy of these programs is short-lasting and most regain the majority of their lost weight. Therefore, current research in this field is highly competitive, essential and focused on dietary intervention. Dietary interventions with plant polyphenols are alternative and promising tools for preventing obesity and metabolic disorders (Meydani and Hasan, 2010; Nijhawan and Behl, 2020; Park et al., 2018; Song et al., 2018). Targets of the antiobesity drug can be divided into two main categories. The first category includes, reduce or limit energy absorption, such as to suppress appetite, pancreatic lipase and alpha-amylase (Williams et al., 2020). The second category consists of a decrease in fat mass by increasing energy expenditure or by redistribution of adipose tissue (Srivastava and

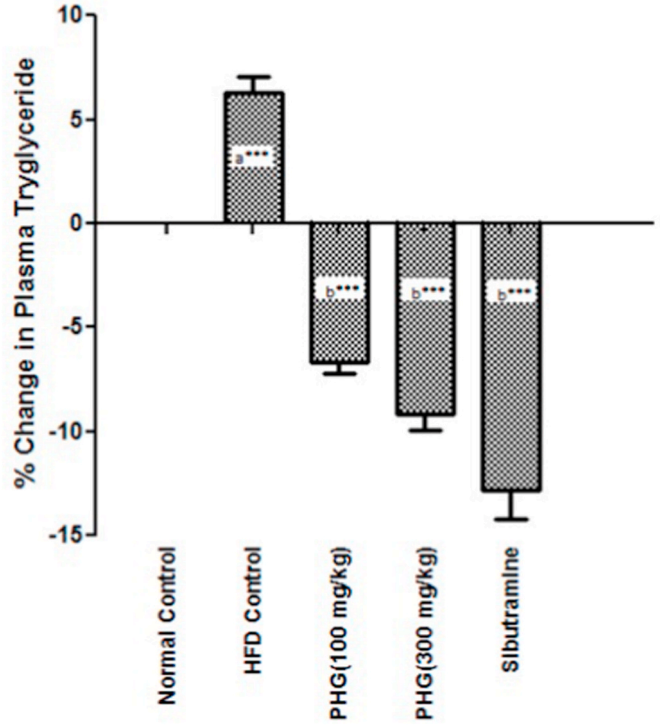

Fig. 1. Effect of PHG on the percentage change of in plasma TG level in rats

The Values are expressed as mean ± SD (n = 6), "a" HFD Control significant compared to Norma Control whereas "b" PHG and Sibutramine treated compared to HFD control group. ***p < 0.001, **p < 0.01 *p<0.05 ^{ns} p>0.05.

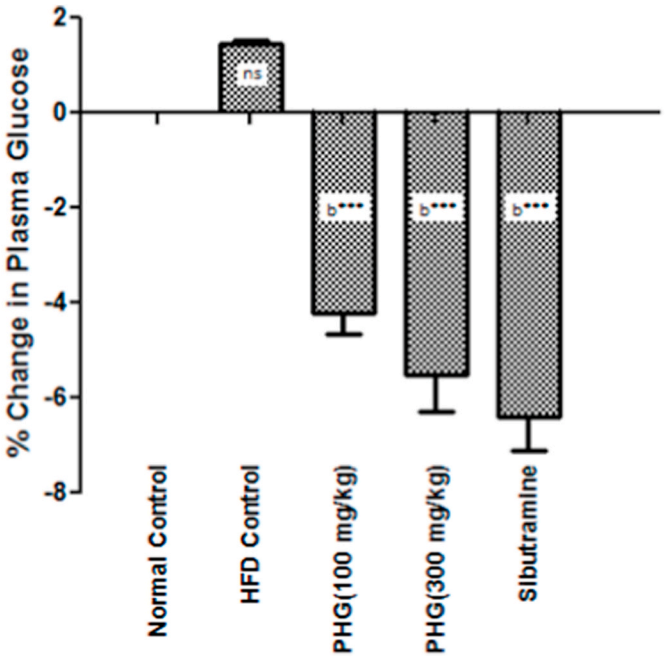

Fig. 2. Effect of PHG on the percentage change of in plasma glucose level in rats

The Values are expressed as mean ± SD (n = 6), "a" HFD Control significant compared to Norma Control whereas "b" PHG and Sibutramine treated compared to HFD control group. ***p < 0.001, **p < 0.01 *p<0.05 ^{ns} p>0.05.

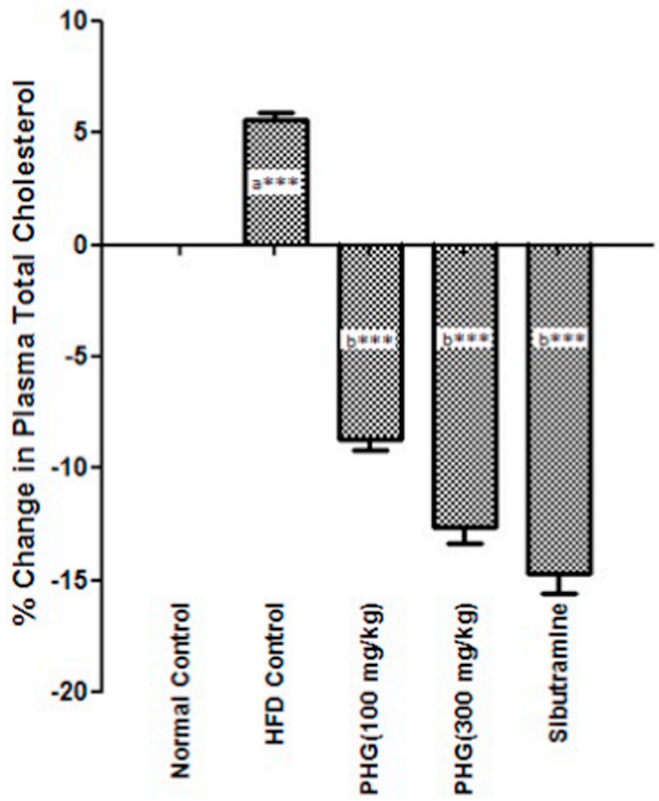

Fig. 3. Effect of PHG on the percentage change of in plasma TC level in rats

The Values are expressed as mean ± SD (n = 6), "a" HFD Control significant compared to Norma Control whereas "b" PHG and Sibutramine treated compared to HFD control group. ***p < 0.001, **p < 0.01 *p<0.05 ns p>0.05.

Apovian, 2018). The desired therapeutic anti-obesity effect of drugs can be achieved by targeting multiple pathogenic mechanisms of obesity. Rani N et al. (2012) reported that the ethanol extract of *Achyranthes aspera*. inhibiting pancreatic amylase and lipase activity and suppress appetite. The alpha-amylase inhibitor has been characterized and tested in numerous clinical studies which is isolated from *Phaseolus vulgaris* (Udani et al., 2018). Likewise, a novel thiocyclitol, isolated from *Salacia reticulata*, inhibited α-glucosidase in vitro (Oe and Ozaki, 2008). The results also demonstrate that *Vitis vinifera* seed extract inhibits adipogenesis by targeting PPARγ (Zhang et al., 2019). The ingestion of *Camellia sinensis* extract shown to enhance energy expenditure in both animals and people (Kim et al., 2011). In the present study, we prepared and evaluated multi-targeted, ready to eat polyherbal formulation by wet granulation techniques.

It is already proven that diet-induced obesity in rats, shares similar features with human obesity includes weighed more than normal controls, developed substantially more adipose tissue than control rats, acquired the insulin resistance and hyperleptinemia (Czech, 2017; Hariri and Thibault, 2010) The possible mechanisms HFD induced obesity include reduce fat oxidation (Schrauwen and Westerterp, 2000), increase lipoprotein lipase activity (Preiss-Landl et al., 2002) and increased food and energy intake (Clifton, 2019; Forde et al., 2015; Nas et al., 2019; Poppitt and Prentice, 1996; Rolls, 2000). In the current study, the plasma TC, glucose and TG level were significantly higher in HFD induced rats in comparison to control rats. The study result demonstrating that PHG treatment effectively controls TC and TG level in obese rats. Thus, PHG may be valuable for the treatment of hypertriglyceridemia and hypercholesterolemia. Moreover, PHG also reduces adipose tissue and body weight significantly. The possible synergistic antiobesity effect of PHG is due to combining the different herb with

similar therapeutic effect and have a diverse mechanism of action.

5. Conclusion

The combination of plants extracts demonstrated excellent weight and fat reducing effect provided rationale for usage and generates conviction among users as effective formulae for weight management and holds the potential to treat obesity. However, the more detailed phytochemical and clinical study should be carried out to endorse the efficacy in human.

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CRediT authorship contribution statement

Chirag Patel: Conceptualization, Methodology, Writing - review & editing, Software. **Lalita Shahgond:** Writing - original draft, Visualization, Software. **Pankita Ahir:** Investigation, Data curation. **Sanjeev Acharya:** Validation, Writing - review & editing, Supervision.

Declaration of competing interest

None'.

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