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Original Research Article

Pharmacological evaluation and antifertility activity of *Aloe barbadensis* linn on female wistar rats.

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Abstract

Ethanolic and Aqueous extract of Leaf of *Aloe barbadensis* was study, antifertility activity in proven fertile female Wistar Rats at the doses 500mg/kg b.wt./day for 30 days. Different parameters were studied in female wistar rats including effect of Reproductive outcome, Antimplantation, Abortifacient study and Estrogenic and Anti-estrogenic activity, Phytochemical were observed.

Aloe vera Leaves shown positive test for Alkaloids, Steroid, Flavonoids, Terpene, Carbohydrates and Tannin. The extract of Aloe vera has anti-fertility effect the control rats showed good number of litters. Treatment of animal with different extracts, resulted a significant (P< 0.05, P< 0.01). antifertility activity (42.2% and 7.8%) was exhibited by AAV and WAV respectively. After 21 days of the extracts free period, the antifertility effect of the extracts was reversed. The extract treatments with AAV, an increase in the resorption index (%) by the extract is an indication of failure in the development of the embryo. The mean percentage of anti-implantation and percent resorption (abortifacient) were found to be highest for AAV-29.46%, WAV -12.17, and AAV-32.96%, WAV-7.78% respectively. The decrement in implantation caused by the extracts may be due to estrogenic or anti-estrogenic activity. However, along with standard AAV exhibiting more potent estrogenic and less potent anti-estrogenic when compared with standard. Clinical assessment of Female antifertility agents should include acceptability, safety and efficacy during and after the treatment. The present study was therefore carried out to evaluate the claimed antifertility effect of Aloe vera leaf using different aspects of reproductive physiology in female wistar rats.

Keywords: Herbal Contraceptive, Antifertility, Reproductive outcome, Anti-implantation, Abortifacient, Estrogenic and Anti-estrogenic.

Introduction

Fertility control is an issue of global and national public health concern. There is a global need to support individuals in family planning due to the increasing growth rate of the world's population with its negative impact on environment, economic growth and poverty reduction in underdeveloped countries. About 90% of the world's contraceptive users are women. Though considerable progress has been made in the development of highly effective, acceptable and reversible methods of contraception in females, progress and possibilities on males are still slow and limited [1]. Aware of this responsibility, health organizations and pharmaceutical companies continue to financially support or actively pursue research towards new contraceptive approaches [2,3]. Current methods of contraception result in an unacceptable rate of unintended pregnancies and many side effects also [4].

Herbal drugs are the therapeutic herbs used to prevent and treat diseases and ailments or to support health and healing. *Aloe vera* (also known as *Aloe Barbadensis*) contains over 200 active components including vitamins, minerals, amino acids, enzymes, polysaccharide, and fatty acids-no wonder it's used for such a wide range of remedies Herbal drugs are the oldest form of health care known to mankind. Fertility regulation with plant preparations in indigenous systems of medicine has been reported in ancient literature 4. A number of plants species have been tested for fertility regulation years ago and were subsequently fortified by national and international agencies [5,6].

Therefore, in the present investigation, herbalism and its efficacy as anti fertility activity will open new avenues to scrutinize rich natural resources for further analysis in order to develop the potential of herbal medicine 6. Such screening and scientific validation may provide the basics for developing novel antifertility without possible side effect [7].

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Methods and Materials

Collection of Plant Material

The Plant specimens for the study were collected from the Satpura region of Madhya Pradesh, India, identified and authenticated by NISCAIR (National Institute of Science Communication and Information resources, New Delhi, A voucher specimen no. is (NISCAIR/RHMD/Consult/2015/2903/102-1). Care was taken to select healthy fully grown plant and normal parts. The samples of different parts were cut suitably and removed from the plant and thoroughly washed with water to remove the adherent impurities and dried in sunlight [8].

Determination of physicochemical parameters

Physicochemical parameters of Aloe vera *Leaf* were determined and reported as total ash, water-soluble ash, acid-insoluble ash Alcohol and water-soluble extractive values were determined to find out the amount of water and alcohol soluble components.

Successive solvent extraction

The method is based on the extraction of active constituents present in the drug, using various solvents ranging from non-polar to polar. The solvents used were Petroleum Ether, Ethanol and Aqueous. Crude drug was subjected to soxhlet extraction with 1.5 litters of each solvent depending on their polarity. Each time before extraction with next solvents the marc was air-dried [9]. All the extracts were concentrated by distilling the solvent at low temperature. They were then weighed and percentages of different extractive values were calculated with respect to air-dried substance [10].

Phytochemical screening

Identification of the chemical constituents were carried out on the powdered Bark of *Aloe vera* and the extract was concentrated and subjected to various chemical tests to detect the presence of different Phytoconstituent [11].

Pharmacological screening

Acute oral Toxicity

The Acute oral toxicity studies were carried out as per the guidelines of Organization for Economic Co-operation and Development (OECD-423), Ministry of Social Justice and Empowerment, Government of India.

Antifertility Study

Antifertility activity of plant extracts were evaluated with the help of reproductive outcome, anti-implantation, abortifacient, estrogenic and anti-estrogenic study was also performed, which further supported by the hormonal analysis [12-15].

Reproductive Outcome In Rats

Three groups of mature female rates (five rat/group) were selected for received extracts for 8 days and control group received vehicle for the same period. All the experimental rats were then allowed to mate with mature fertile male rat and the treatment continued for 21 days. The number of litters was determined after the completion of one gestation period in all-experimental groups. The litters were allowed to grow and the growth of litters produced from the extract-administered group was compared with those of control group. The reversibility of antifertility effect of the extracts was also studied in the treated groups. For this study, the extracts were administered continuously for 21 days and then the extract was withdrawn. After 21 days of extracts withdrawal, animals were allowed to mate with male rate. The number of litters was determined after the completion of one gestation period.

Anti-implantation study

Estrous cycle studies, proven fertile female Wistar rats, weighing between 150 and 200g were selected and left overnight with male of proven fertile in the ratio of 3:1. The extracts were administered orally to separated group rats at the dose level of 500 mg/kg from day 1 to day 7 of pregnancy. Control animal received the vehicle (CMC 0.5%). The animals were then laparotomised on day 10 of the pregnancy under excess dose of thiopentone sodium and uteri were examined to determine the number of implantation sites.

Abortifacient study

Female rats at first day of pregnancy were divided into three groups, consisting of (5-6) animals in each group. The animals were laparotomised under light ether anaesthesia and semi-sterile conditions on 10th day of pregnancy. Both horns of the uterus were observed for the number of implants. The rats were sutured and allowed to recover. The first group served as control and received vehicle only (Tween-80, 1%) and group second and third received suspension of extract at a dose of 500 mg/kg b. wt. in 1% Tween-80, respectively, from day 10 to 18 of pregnancy. During the experiment, animals were observed for vaginal bleeding. On 21st day, animals were laparotomised under light ether anaesthesia and observed for number of litters and percentage of resorption compared with initial number of implantation observed on 10th day of pregnancy.

Estrogenic and antiestrogenic study

Colony breed immature ovariectomised female rats (21-23 days) weighing between 25 and 30 g were used. They were divided into experimental and control groups, consisting of six animals each group. The extracts were suspended in 0.5% CMC and administered orally for 7 days at the dose level of 500 mg/kg body weight. Ethinyl estradiol (Unicure Remedies Pvt. Ltd., Baroda, India) in olive oil 1 µg/rat per day was injected subcutaneously for 7 days in another group to induce estrous. CMC 0.5% was administered orally to the control animals. The extract at the dose level of 500 mg/kg was also administered orally along with ethinyl estradiol in olive oil at 1µg/rat per day subcutaneously to different groups of rat for the same period. On the 8th day of the experiment, all the animals were sacrificed by decapitation under light ether anaesthesia and the uteri were dissected out, surrounding tissues removed, blotted on filter paper and weighed quickly on balance sensitive to 0.0001 g. A portion of the uterine tissues and adrenal glands from the control and treated animals were fixed in Bouin's fluid for 24 h, dehydrated in alcohol and then embedded in paraffin. The paraffin blocks were sectioned at 6 mm intervals and stained with haematoxylin-eosin for histological examinations.

Hormonal Analysis

Hormonal Analysis were determined by Merck Kit method (Merck cat # 15891) by using microlab-300 IX Merck apparatus

(Autoanalyser). Blood (2ml) was drawn by retro-orbital puncture and was immediately transferred into EDTA coated vacationer. The samples were mixed gently and were left for more than half an hour at room temperature, and finally centrifuged at 3000 rpm for 15 minutes. Serum was separated and assayed for FSH, LH, 17 β -estradiol, prolactin and 17-OH progesterone using enzyme linked immunoassay (EIA) technique. [Elisa reader (BIORAD 680 Microplate Reader)[16-17].

Statistical Data

All values are expressed as mean ±sem. Means were statistically analyzed by one-way analysis of variance (ANOVA), and values of P<0.05 were considered statistically significant.

Result and Discussion

Physicochemical Parameters

Physicochemical parameters of *Aloe vera* leaf were determined. In physicochemical parameter total ash is approximately seven times and four times more than acid insoluble ash and water soluble ash respectively [18]. Ethanol soluble extractive is approximately two times higher than water soluble extractive. Moisture content was less than 7.6 % and pH was 6.8. ware shoe in table 1.

Physicochemical Parameter	Value % w/w* Mean± SD.
Total Ash	14.5 ±0.5% w/w
Acid insoluble ash	1.90±0.1% w/w
Water soluble ash	3.75±0.2% w/w
Water soluble extract	3.75±0.3% w/w
Ethyl alcohol soluble extract	7.0±0.3% w/w
Moisture content	7.6%
pH	6.8

Table 1: Various physicochemical parameters

w/w*- weight/weight.Value (%) Mean±S.E.

Preliminary Phytochemical Investigation

A number of phytoconstituent from natural sources have been proved efficacy to prevent the pregnancy. Many scientific reports were published for antifertility activity of Flavonoids Glycosides, Alkaloids, Steroid. Phytochemical investigation of *Aloe vera showed* (Table 2) the preliminary phytochemical study of *Aloe*

veraleaf showed that Alkaloid, Steroid, Flavonoid Glycoside, Tannin, was present in Alcoholic Extract. Whereas, Steroid, Terpene, Tannin were present in Petroleum Ether Extract and Terpene, Glycoside and Tannins were present in Aqueous Extract. The successive solvent extraction with petroleum ether, alcohol and water gave 3.5%, 7.4% and 5.4% practical yield.

Test for Constituent Aloe veraleaf Petroleum Ether Extract (P.E.E) Alcoholic Extract (A.E). Aqueous Extract (W.E.) Alkaloid -ve +ve -ve Steroid +ve +ve -ve Terpene +ve -ve +ve Flavonoid -ve +ve -ve Glycoside +ve +ve +ve Sugars -ve +ve +ve Saponins +ve -ve -ve Tannin +ve +ve +ve Carbohydrate +ve +ve -ve Colour and Consistency Green colour Brownish green colour Dark green Yield 3.5% 7.4% 5.4% PAV AAV WAV Code

Table 2: preliminary phytochemical study of Aloe vera Leaf

Whereas code PAV-Petroleum Ether Aole Vera Extract, AAV-Alcoholic Aole Vera Extract and WAV-Aqueous Aole Vera Extract

Acute oral toxicity

Acute toxicity studies were carried out to evaluate toxicity and to determine the minimum lethal dose of the drug extracts, using Wistar Rats. No clinical signs were evident in any animal during treatment period. (Clinical observations include changes in skin and fur, eyes and mucous membranes, and also respiratory, circulatory, autonomic and central nervous systems, and somatomotor activity and behavior pattern, tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma). No mortality as well as any clinical sign of toxicity has been observed at a dose level of 2000 mg/kg indicating that all the extracts comes under category 5 and hence, LD50 cut-off was found to be 2000 mg/kg body weight. Hence, one-five of this dose, i.e. up to 500 mg/kg body weight, was used for antifertility investigation. Heamatological and biochemical parameters were also performed before and after treatment and no significant changes were observed [19].

Reproductive outcome study

Table 3 shows the effect of different extracts on the fertility of female rats. The control rats showed good number of litters. Treatment of animal with different extracts. resulted a significant

(P< 0.05, P< 0.01). A significant antifertility activity (42.2% and 7.8%) was exhibited by AAV and WAV respectively.

It was also found that the litters of the extract treated rats did not show any physical deformity. All litters grew up to normal adult stage, which indicates that the extracts do not have teratogenic effect and the absence of teratogenic effect of extracts at a given dose justifies the safety of the plant. The present observations agree with [20], who reported the reversible antifertility effect of *Ricinus communis* (castror beans) on female rabbits, and also supported by [21], who reported the same effect of the methanolic root extract of *Rumex steudelii* on female rats.

After 21 days of the extracts free period, the antifertility effect of the extracts was reversed for all animals. An increase in the number of litters observed in all the post treatment groups may indicate the reversible antifertility effect of all extracts. These observations correlate the findings of Ganguly *et al.* (2007) and Gebrie *et al.* (2005) who reported the reversible antifertility effect with similar observations on the treatment with methanolic extract of *Cissampelos pareira* leaves in mice and methanolic root extract of *Rumex steudelii* in rats respectively. The animal groups gave 9.06 \pm 0.15 litters at an average. This showed that there was no statistically significant change from the control group (10.00 \pm 0.03).

Table 3: Effect of Extracts on Reproductive Outcome

Table 6: Enest of Extracte of Trepreductive extreme			
Group	Oestrous Cycle	Fertility	Litters Present
Control	Regular	100 % + Ve	10.00 ± 0.03
AAV	Irregular	42.2% - Ve	5.78 ± 0.10 a
WAV	Irregular	7.8% - ve	9.22 ± 0.15 ^b
W.D-AAV	Regular	80.5 % + Ve	8.05 ± 0.05 a
W.D-WAV	Regular	84.5 % + Ve	8.45 ± 0.25 b

Whereas AAV: Alcoholic *Aloe vera* Extract, WAV: Aqueous *Aloe vera* Extract, W.D-AAV: withdrawal Alcoholic *Aloe vera* Extract and W.D- WAV: withdrawal Aqueous *Aloe vera* Extract. Values are expressed as mean ± S.D.P values a = P < 0.05, b= P < 0.01, when compared with normal control

Anti-implantation and abortifacient activities

Postcoital antifertility study showed the anti-implantation activity in the treated animals. Treated animals delivered litters which, was significantly less than control (Table 4). The extract treatments with AAV, significantly (P<0.001) reduced the number of litters born (Table 4). This indicates the abortifacient nature of extracts. An increase in the resorption index (%) by the extract is an indication of failure in the development of the embryo (Dhanwad *et al.*, 2005). Such occurrence of foetal resorption suggests that interruption of pregnancy also occurred after implantation (Elbetieha, 2000). These observations indicate the pregnancy terminating potential of the extract. Embryonal resorption could be due to modifications of uterine lining function or maternal toxicity which consequently may

increase early resorption and late fetal death (Chaves, 1985; Khera, 1987). Hence, the present investigation clearly reveals that the extracts are effective before and after the implantation occurs (Vasudeva and Sharma, 2006).

Both these activities were calculated on the basis of number of implants and number of litters. The mean percentage of anti-implantation and percent resorption (abortifacient) were found to be highest for AAV-29.46% and WAV12.17, whereas in the case of percent resorption; AAV-32.96% and WAV-7.78%, These results (show Table 4 and Table 5) indicated that all the extracts inhibited the conversion or development of implants into litters. The decrement in implantation caused by the extracts may be due to estrogenic or anti-estrogenic activity as described by Hafez (1970).

Table 4: Effect of Extracts on Anti-Implantation Activity

Treatment	ANTI-IMPLANTATION ACTIVITY		
(Dose)	No. of implants	No. of litters	Mean % anti-implantation
Control	7.23 ± 0.52	7.20 ± 0.65	Nil
AAV	5.10 ± 0.89	5.08 ± 0.22	29.46
WAV	6.35 ± 0.43°	6.05 ± 0.10 a	12.17

Values are expressed as mean \pm S.D. P values a = P < 0.05, b= P < 0.01,

Table 5: Effect of Extracts on Abortifacient Activity

Treatment	Abortifacient Activity		
(Dose)	No. of implants	No. of litters	% resorption
Control	7.32 ± 0.62	7.10 ± 0.30	3.00
AAV	5.40 ± 0.52	4.95 ± 0.42	32.96
WAV	6.85 ± 0.20	6.75 ± 0.42	7.78

Values are expressed as mean ± S.D.

P values a = P < 0.05, b = P < 0.01, when compared with normal control

Estrogenic and anti-estrogenic study

Antifertility activity of all the extracts were finally evaluated with the help of estrogenic and anti-estrogenic activity associated with hormonal level and histological parameter like uterine weight, diameter of uterus, thickness of endometrium and height of endometrium epithelium. The stages of estrous cycle and its duration were determined as described by Makonnen et al. (1997). The detail data has given in Table 6 and Table 7. The uterotropic potency, in terms of the weight of uterus, AAV (Alcoholic Extract of Aloe vera) were found to be 61.25%, and WAV (Aqueous Extract of Aloe vera) were found to be 43.24%, when compared with standard (ethinyl estradiol). The Number of cornified cells in vaginal smears was considerably higher (+ to ++) than that of controls (0 to +), but notably less than that of ethinyl estradiol-treated rats (+++). All the treated rats showed open vagina. Oral administration of AAV and WAV alone at a dose level 500 mg/kg body weight, AAV show highly significant (P < 0.001) change in uterine weight, thickness of endometrial epithelium and height of endometrial epithelium when WAV show less significant (P < 0.001) as compared with that of control.

However, along with standard AAVexhibiting strong estrogenic property, increase in uterine weight, diameter of uterus, thickness of endometrium and height of endometrial epithelium and WAV exhibiting strong anti-estrogenic property, decrease in uterine weight, diameter of uterus, thickness of endometrium and height of endometrial epithelium when compared with standard. These observations are similar to the finding of Ravichandran *et al.* (2007) and Vishnukant and Rana (2010) on the effect of hydroalcoholic extract of *Ailanthus excels* (Roxb.) stem bark and *Plumbago zeylanica* leaves on uterus of female Wistar rats. These observations revealed that these extracts acted as competitive antagonist to ethinyl estradiol. Hence, the anti-implantation activity of these extract may be due to their anti-estrogenic nature, which antagonise the action of estrogen and cause structural and

functional changes in uterus and finally decreases the implantation

[21,22].

Table 6: Effect of Extracts on Estrogenic and Anti- Estrogenic Study

Treatment (Dose)	Uterine weight (mg/100 g body weight; mean ± S.D)	Vaginal cornification
Control	70.24 ± 5.35^a	NIL
Ethinyl Estradiol (1 µg/rat per day)	335.40 ± 7.56 ^a	+++
AAV (500 mg/kg)	205.45 ± 5.13	+ to ++
WAV (500 mg/kg)	145.05±0.25 ^b	++
Ethinyl estradiol (1 µg/rat per day) +AAV (500 mg/kg)	386.83 ± 5.87 ^a	+++
Ethinyl estradiol (1 µg/rat per day) +WAV (500 mg/kg)	185.02 ± 4.40	+

Values are expressed as mean ± S.D.

P values a = P < 0.05, b = P < 0.01, c = P < 0.001 when compared with normal control whereas +: Nucleated Epithelial Cells, ++: Nucleated Epithelial Cells, and Cornified Cells, ++: Cornified cells.

Table 7: Histological Changes in the Uterus and Endometrium after Treatment with Extracts

Treatment (Dose)	Diameter of uterus $(\mu m \pm S.D)$	Thickness of endometrium (µm ± S.D)	Height of endometrial epithelium(µm ± S.D)
Control	330.54 ± 5.25 a	54.14 ± 2.12	17.4 ± 0.25^a
Ethinyl Estradiol (1 µg/rat per day)	821.25 ± 6.25 °	245.45± 15.15 ^c	45.10 ± 4.18 ^c
AAV (500 mg/kg)	465.17± 4.66	194.01 ± 5.50 ^c	25.00 ± 4.43^{b}
WAV (500 mg/kg)	217.24 ± 1.05	90.24±4.08	22.45±4.52
Ethinyl Estradiol (1 μg/rat per day) +AAV (500 mg/kg)	825.17 ± 4.66	248.01 ± 5.50 ^c	45.02 ± 4.43^{b}
Ethinyl Estradiol (1 µg/rat per day) +WAV (500 mg/kg)	425.28± 01.25°	95.09± 6.24 ^b	25.02± 4.14 ^a

Values are expressed as mean ± S.D.

P values a = P < 0.05, b = P < 0.01, c = P < 0.001 when compared with normal control

Hormonal analysis

Sex hormones were assayed based on their roles in maintaining pregnancy, since a failing pregnancy could be correlated to the levels of these hormones in the body fluids (Yakubu and Bukoye, 2009). The reduction in the concentration of FSH is an indication of disturbance of estrus cycle and ovulation (Ganguly *et al.*, 2007). LH is required for continued development and normal function of corpora lutea. The significant reduction in the level of serum LH could be associated with the physiological process of luteolysis preceding parturition (Yakubu and Bukoye, 2009). It could possibly be attributed to pregnancy failure resulting from a luteal phase that is not being maintained. The reduced level of hormone may also be due to inactivation of lutenization of ovarian follicles, which could be responsible for the reduction in the concentration of serum

progesterone in this study [23-26]. Elevated level of progesterone during pregnancy plays a key role in maintaining the conditions and is an important factor in the implantation process. Therefore, luteolysis and reduction in the blood levels of progesterone may contribute to abortion and anti-implantation activity of the all extracts [27-32]. The findings of present study were agreed with previous studies which reported the effect of *Inula viscose* and *Bambusa vulgaris* eaf extract on implantation and abortion in rats and rabbits (Yakubu and Bukoye, 2009). In this study, an increase in prolactin level was observed (Table 8), These findings were also supported by Ganguly *et al.* (2007), who reported that a combination of enhanced prolacin and suppressed LH secretion is due to prolongation of estrus cycle (Ganguly *et al.*, 2007). An imbalance in endogenous estrogen and progesterone levels could be responsible for Anti-implantation activity (Dhanwad *et al.*, 2005).

Table 8: Hormonal Levels in Various Groups of Animals

Treatment 500mg/kg	LH	FSH	Prolactin	17β estradiol	17 OH Progesterone
Control	6.25±2.42	8.64±5.20	40.25±6.10	745.12±45.40	14.54±1.10
AAV	4.10±4.17	5.16±2.05	40.70±3.20	587±14.42	25.14±4.10
WAV	3.20±4.10	4.14±1.14	26.15±2.20	430±02.02	18.02±2.05

N=5, Data representation as Mean±SD

P values a = P < 0.05, b = P < 0.01, c = P < 0.001 when compared with normal control

Conclusion

The present findings inferred that the gathering treated with the most noteworthy convergence of plant concentrate indicated great come about as that of the standard medication and was underpinned by histopathological investigations of the antifertility activity on female Wistar rats. Antifertility activity of plant extracts was evaluated with the help of reproductive outcome, antiimplantation, abortifacient, estrogenic and anti-estrogenic study was also performed, which further supported by the hormonal analysis. It is well known that for implantation exact equilibrium of estrogen and progesterone is essential and any disturbance in the level of these hormones may cause infertility. In our study clearly demonstrates that Extract of Aloe vera leaf, the control rats showed good number of litters. Treatment of animal with different extracts. resulted a significant (P< 0.05, P< 0.01). A significant antifertility activity (42.2%) was exhibited by AAV. It was also found that the litters of the extract treated rats did not show any physical deformity. All litters grew up to normal adult stage, which indicates that the extracts do not have teratogenic effect and the absence of teratogenic effect of extracts at a given dose justifies the safety of the plant. After 21 days of the extracts free period, the antifertility effect of the extracts was reversed for all animals. An increase in the number of litters observed in all the post treatment groups may indicate the reversible antifertility effect of all extracts.

Estrogenic in nature at the dose of 500mg kg ⁻¹ bodyweight as evident form the along with standard, AAVAlcoholic Extract significance increases in the diameter of uterus, height of endometrial epithelium, and thickness of endometrium in extracted animal, while along with standard, WAV aqueous extract 500mg kg ⁻¹ bodyweight showed less Anti-Estrogenic in nature decrease in the diameter of uterus, height of endometrial epithelium, and thickness of endometrium in extracted animal. It is a suitable plant for developing antifertility drug *Aloe vera* is recommended for working out and should be experimented for antifertility program me. Further studies on mechanism of antifertility action and isolation of the active components responsible for antifertility effect are in progress.

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