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Design and Development of Polyherbal Formulation for Arthritis

Mishra Saurabh

Department of Pharmacy, M.J.P. Rohilkhand University, Bareilly-243006, (Uttar Pradesh), India.

ABSTRACT

From long back herbal drugs are used for treatment of arthritis and other joint disorders which require potent analgesic and anti-inflammatory action together with pharmacological activities which can induce the remission by modifying the course of the disease. Our ancient text of Ayurveda like Charak Samhita, Charak Sutrasthan, Sushrut Sutrasthan, Bhavprakash, Rajnighantu prescribe the use of different Herbo-mineral agents in such diseased conditions, which gives a vision to different researcher to investigate the plant component and their pharmacological action for their therapeutic use.

The present work is focused on the development of new polyherbal anti-arthritic formulation by carefully selecting few herbs for treatment of arthritis, which may full fill the criteria of Herbal combination therapy i.e. provide synergistic action without any interaction so that less dose may be required and different organ or system affected by the disease can be targeted with focus on joint inflammation and pain. To achieve this objective four drugs were selected, which were already reported for their potent anti-rheumatic and anti-inflammatory activity i.e. Guggal, Sunth, Arand, Giloe and two diuretic drugs i.e. Gokhru and Punarnava are added in the formulations, which helps in treatment of associated disorders. The combination suitability was derived from the Ancient literature consulting Ayurvedic physicians. Finally the tablet dosage form was prepared from a developed Polyherbal formulation. Four different batches are prepared by changing the binder in tablet formulation and evaluated for standard quality parameters for the tablet.

Key Words: Arthritis, Ayurvedic, Polyherbal, Formulations, Extract, Tablet

INTRODUCTION

The demand for herbal medicines or Therapeutic agents based on natural product is continuously increasing for chronic disease not only in India but also in western countries. During last two decades, the consumption of medicinal plant has almost doubled in western countries. Plant products contribute about 25% of medicine used in the country and it is estimated that herbal drugs form the basis for the health care need of 64% of world population. The reversal of herbal products is a worldwide phenomenon now a day's mainly due to two reasons, one is that no new major lead is coming up and second is the sensitization reactions and undesirable side effects are associated with the synthetic compounds.¹ In recent past a large number of herbal base therapeutic agents were launched in Indian market, which has become very popular within a short period of time.

The joints are subjective to a wide variety of disorders including degenerative changes, infections, autoimmune diseases,

metabolic degradation and neoplasm. Arthritis is a chronic inflammatory illness of joints being capable of producing severe crippling deformities and functional disability.² It is an autoimmune disease in which the immune system attacks normal tissue components as if they were invading pathogens. This illness affects about one percent of the world's population.³ The different types of arthritis are Rheumatoid arthritis, Degenerative joint diseases, Infectious arthritis and Gout. The main symptoms are Joint swelling, Joint tenderness, stiffness, and pain especially in the small joints of the hands and feet.⁴

Arthritis has long been considered as the "traditional" treatment option. Because it is a chronic disease, the therapy requires long-term treatment and management. Most of the drugs used have potential side effects and adverse reactions and individual response to drugs can vary because of disease status of patients and other associate diseases in patient. The drug therapy for arthritis is focused on firstly to relieve pain,

Corresponding Author:

Mishra Saurabh, Department of Pharmacy, M.J.P. Rohilkhand University, Bareilly-243006, (Uttar Pradesh), India.
E-mail: saurabhmcm2002@gmail.com

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inflammation and muscle stiffness and also to modify the course of the disease or induced remission.

Various NSAIDs and COX-2 Inhibitors along with SAARD (slow-acting antirheumatic drugs) and DMARD (Disease-modifying Anti rheumatic drugs) are used for the treatment of arthritis. Even multiple drugs of different category are available for the treatment but still, the arthritis is incurable; only the maintenance and delaying of symptoms are the strategy of treatment. For this reason, the herbal therapy is most attractively and commonly used for this disease which also reduces the side effect load in the patients.⁵

Various plants are reported and widely used for their anti-inflammatory and anti-arthritis activity.⁶ Some important plants are selected for development of herbal formulation development. Four anti-inflammatory herbs were selected for development of herbal formulation i.e. Guggal, Sunth, Arand and Giloe and two diuretic drugs i.e. Gokhru and Punarnava were added in the formulations, which helps in the treatment of associated disorders. The combination suitability was derived from the ancient literature of Ayurveda i.e. Charak Samhita, Bhavprakash, Sushrut Sutrasthan and consulting with Ayurvedic physicians.

MATERIALS AND METHODS

The crude drug materials were purchased from local herb supplier and it was characterized by evaluating the quality of raw material as specified in Indian Pharmacopoeia 1996; Indian Herbal Pharmacopoeia 2002 and as per WHO guidelines for quality control of medicinal plants. Quality parameters stated in the individual monograph of drug in Indian Herbal Pharmacopoeia 2006 was taken as standard for evaluation purpose.

For preparation of Polyherbal Formulation for Arthritis six herbal Drugs were selected after review of literature and consultation with Ayurvedic Physicians. The drugs selected were **Guggal** (*Commiphora wightii*), **Sunth** (*Zingiber officinales*), **Arand** (*Ricinus communis*), **Giloe** (*Tinospora cardifolia*), **Ghokhru** (*Tribulus terrestris*), **Punarnava** (*Boerhavia diffusa*). The individual drug reference suggests that these six drugs can be used for the treatment of joint and inflammatory disorders in powdered as well as aqueous extracts form so these six drugs candidates were selected for the development of rational poly-herbal anti-arthritis formulation.^{7,8}

Formulation Rationale

The herbal combination therapy is based on two basic principles i.e. The drug used in combination must possess synergistic and there should not be any interaction among them. The synergistic effects of above six herbal drugs have already

been reported in the form of different formulations in ancient literature, which also strengthen use of above drugs in a single formulation. (Bhaishaijya Ratnawali, Ayurved Sar-Sangrha).⁹ Over and above suitability of combination was consulted with some renowned Ayurvedic Physicians also.

One most important approach in designing formulation is that the herbs used not only provide the analgesic and anti-inflammatory effect for treatment of joint swelling and pain but also relieve the patients with associated disorders like constipation, lower gastric tolerance for other drugs, uric acid deposition etc.

Table 1: Major and Supported therapeutic actions of drug candidate used in Polyherbal Formulation

Sr. No.	Drugs in formulation	Major therapeutic Action of ingredient	The supported therapeutic action of ingredient for combination
1.	Guggal (20%)	Anti-rheumatic Potent anti-inflammatory	Anti-ulcer, Carminative Cholagogue
2.	Sunth (20%)	Anti-rheumatic	
3.	Arand (20%)	Potent anti-inflammatory	Cathartic, Hepatoprotective
4.	Giloe (20%)	Anti-Rheumatic	Anti-oxidant
5.	Gokhru (10%)	Anti-Rheumatic Analgesic	Immunostimulant, anti-pyretic
6.	Punarnava (10%)	Diuretic Antiurolithiatic Diuretic	- Hepatoprotective

The Proportion of six ingredients in

The developed Poly herbal formulation contains Guggal 20%, Sunth 20%, Arand 20%, Giloe 20%, Gokhru 10% and Punarnava 10%. The combination contains the drugs in equal proportions. Here the ratio of Punarnava and Gokhru were reduced because of their same therapeutic action in combination, which is a supported action required in case of the proposed formulation. The normal doses of the above formulation will be 2gm/day in human which is also derived from the reported literature but dose titration can be done 2-4 gm/day according to severity of disease (The Ayurvedic pharmacopoeia of India, 2003). This is supposed that the different drugs used in the combination will act by different mechanism of action that can be understood by meticulous pharmacological studies of the formulation.

Identification and characterization of Herbal drugs

Drugs were Identified and characterized for the following parameters as per WHO guidelines for quality control of medicinal plants and Indian Herbal Pharmacopoeia 2002 to determine quality, purity and detection of nature of adulteration.^{10,11,12}

Detection of Foreign matter

100-500g or quantity specified in the individual monograph of the original sample was weighed and spread into a thin layer. Sample was inspected with unaided eye and a 6x lens and foreign matter was separated manually as completely as possible. The percentage of foreign matter was calculated by weighing the amount recovered with reference to air dried drug.^{10,11}

Ethanol soluble Extractives

5g of air-dried drug was coarsely powdered and macerated with 100 ml. of ethanol in a closed flask for 24 hours; frequently shaking was done during first 6 hour and then allowed to stand for next 18 hours. Thereafter it was filtered rapidly taking precautions against loss of ethanol. 25 ml. of filtrate were evaporated to dryness in tarred flat-bottomed shallow dish, dried at 105°C and weighed. The percentage of ethanol soluble extractive was calculated with reference to the air dried drug.^{11, 13}

Water-soluble Extractives

5g of drug was added to 50 ml. of water at 80°C in a stoppered flask. Flask was shaken and allowed to stand for 10 min. Then this was cooled and 2g of kieselgur was added and filtered. 5ml. of the filtrate was transferred to a tared evaporating dish (7.5cm diameter). Solvent was evaporated on the water bath and dried for 30 minutes. Finally, it was dried in steam oven for 2 hour, and residue was weighed. Percentage of water soluble extractive was calculated with reference to the air dried drug.^{10, 13}

Total Ash

3g of the air-dried crude drug was accurately weighed in silica dish, and then sample was incinerated at a temperature not exceeding 450°C until free from carbon, cooled and weighed. If the carbon-free ash was not obtained in this way the charred mass was exhausted with hot water and residue was collected on ashless filter paper. Residue and filter paper was incinerated until the ash is white or nearly so. It was added into filtrate and evaporated to dryness and ignited at temperature not exceeding 450°C. Percentage of ash was calculated with reference to the air dried drug.^{10, 11, 13}

Acid Insoluble Ash

Ash obtained from the procedure mentioned in the total ash was boiled with 25 ml. of 2M hydrochloric acid for 5 minutes. Insoluble matter was collected on ash-less filter paper. It was washed with hot water, ignited, cooled in desiccators and weighed. Percentage of acid-insoluble ash was calculated with reference to the air dried drug.^{10, 11, 13}

After characterization drugs were processed to develop poly herbal formulation.

Preparation of Powder Formulation

Crude drugs were crushed to convert into fine powder. All the fine powdered drugs were passed through sieve no. #44 and mixed together into following proportion (as per table no.3) for proper blending in a blender to develop the powder anti-arthritic formulation.

Table 2: Powder Formulation Matrix- P₁

Sr. No.	Ingredients	Amount Taken (as powder)
1.	<i>Commiphora wightii</i> (Guggal)	10g
2.	<i>Zingiber officinales</i> (Sunth)	10g
3.	<i>Ricinus communis</i> (Arand)	10g
4.	<i>Tinospora cardifolia</i> (Giloe)	10g
5.	<i>Tribulus terrestris</i> (Ghokhru)	05g
6.	<i>Boerhavia diffusa</i> (Punarnava)	05g

The powder prepared by this method have dose of 2g/day, which increase the number of tablet daily taken by the patients. So further process was carried out for reduction in dose by a reduction in volume of powder.^{14, 15} Different drug powder and aqueous extracts was combined in the proportion as per matrix P₂ (table no 4). In this formulation, some drugs was used in the powder form whereas other was absorbed on the powder in aqueous extract one by one. And finally prepared powder was dried under sunlight. By this way overall dosage of the powder reduced to 1g/day which can be easily compressed into tablet of 500mg and should be taken as 2 tablet together.¹⁶

Table 3: Powder Formulation Matrix- P₂

Sr. No.	Ingredients	Amount Taken (as powder)	Amount Taken (as Extracts)
1.	<i>Commiphora wightii</i> (Guggal)	05g	Equivalent to 5g of powder drug
2.	<i>Zingiber officinales</i> (Sunth)	10g	-
3.	<i>Ricinus communis</i> (Arand)	-	Equivalent to 10g of powder drug
4.	<i>Tinospora cardifolia</i> (Giloe)	05g	Equivalent to 5g of powder drug
5.	<i>Tribulus terrestris</i> (Ghokhru)	-	Equivalent to 5g of powder drug
6.	<i>Boerhavia diffusa</i> (Punarnava)	-	Equivalent to 5g of powder drug

Guggal and Sunth extracts were prepared through Maceration Process. 50g of drug was macerated with 250 ml of slightly heated water for 24 hours. Shaking was done occasional and after 24 hours it was filtered, which yields approx 200 ml. of extract. So this extract contains active drug equivalent to 50g of powder. Arand, Gilo, Ghokhru and Punarnava extracts were prepared by decoction process. 50g of drug was decocted with 800ml of water (16 times of drug) by

heating at 100°C, until the water in flask remain up to 200ml. (4 times of drug) and after that it was filtered, which yields approx 200ml. of extract. So this extract contains active drug equivalent to 50g of powder.^{6, 14, 16}

Tablet dosage form development

Firstly the granules were prepared from powder mixture P2 as per tablet formulation matrix table no. 5 using different binders. When guggal was used as aqueous extract in the preparation of power P₂ on drying it was found that it act as good binding agent for tablet powder. The attempt was made to compress the tablet without using binding agent. After complete sun-drying power passed through sieve no. #44, then all the ingredients was mixed properly. Granule G2, G3 and G4 were prepared by wet granulation method using sucrose solution, gum acacia and starch solution respectively as a binding agent and passed through sieve no. #22. Then granules were air dried for 30 min. and finally it was dried in hot air oven for 10 min. at the 30°C. Dried granules were lubricated with talc (0.1%) and Magnesium stearate (0.1%) for increasing the flow property of granules. The lubricated granules were evaluated for granular properties

Table 4 : Tablet Formulation Matrix

Sr. No.	Formulation : Ingredients	G1	G2	G3	G4
1.	Powder mixture P ₂ (#22)	500 mg	500 mg	500 mg	500 mg
2.	Sucrose solution (2.0%)	-	10 mg	-	-
3.	Gum Acacia (2.0%)	-	-	10 mg	-
4.	Starch solution (2.0%)	-	-	-	10 mg
5.	Talc (0.1%)	0.5mg	0.5mg	0.5mg	0.5mg
6.	Magnesium Stearate (0.1%)	0.5mg	0.5mg	0.5mg	0.5mg

Evaluation of granules

Granules prepared by using different binder were evaluated for their flow and compressibility properties. Firstly granular density was evaluated which may influence compressibility, tablet porosity, dissolution and other properties. Dense, hard granules may require for compressible loads to produce a cohesive compact. For determination of Bulk density, an accurately weighed (mass) sample of granule was carefully added to the measuring cylinder with the help of funnel and initial volume was noted and bulk density was calculated by formula (i)

$$P_b = \frac{M}{V_b} \quad (i)$$

P_b = Bulk density, M = Mass (weight) of the powder, V_b = Total Volume of packing.

Tapped Density is the measure of density of granule in tightly packed form and signifies the compressibility of granules. For determination of Tapped density, an accurate weight (mass) sample of granule was carefully added to the measuring cylinder with the aid of funnel, and measuring cylinder was tapped on flat surface in installment of 300, 750 and repeatedly 1250 till no further reduction in volume of powder and final tapped volume (V_T) was noted and tapped density was calculated with help of formula (ii).

$$P_T = \frac{\text{Mass}}{\text{Tapped Volume (V}_T\text{)}} \quad (ii)$$

The Compressibility index is a simple indication of ease with which a material can be induced to flow; it is measured by following equation (iii).

$$I = \left[1 - \frac{V}{V_0} \right] \times 100 \quad (iii)$$

I = Compressibility index, V = Volume occupied by a sample of powder after being subjected to standardized tapping procedure, V₀ = Volume before trapping

Value of I below 15% usually give rise to good flow characteristic, but reading above 25 indicate poor flowability.¹⁷

For measurement of Angle of Repose the fixed funnel and free standing cone method was used which employed a funnel that was secured with its top at a given height H above a graph paper that is placed on horizontal surface. Granules were transferred carefully through the funnel to make a pile. The Circular line was drawn on graph paper to calculate the radius of the pile and angle of repose was calculated by following formula (IV).¹⁷

$$\tan \phi = \frac{H}{R} \quad \phi = \tan^{-1} \frac{H}{R} \quad (IV)$$

H = Height of pile, R = Radius of pile, θ = angle of repose.

Value of angle of repose ≤ 30° usually indicate a free flowing material, whereas value of angle of repose ≥ 40° usually indicate poorly flowing material.

Tablet compression

Granules prepared in different batches (G1-G4) was mixed with Talc and Magnesium stearate and compressed into tablet with the help of Cadmach rotary tablet press 8 station, by using 15 mm, concave plain punch.

Evaluation of tablet:

The tablets prepared by above method were evaluated for following parameters:

Uniformity of weight: 20 tablets of each batch (G1-G4) were selected randomly and individual weight of each tablet was determined with the help of balance. Average weight of

20 tablets was calculated and deviation of individual weight from the average weight was measured in percentage.¹³

Hardness test: Tablet hardness has been defined as the force required to break a tablet in a diametric compression test. The tablet are crushed between two anvils and the forced applied to break is recorded. It is also termed as crushing strength of tablet. In the present study the hardness of tablets was measured by using “Monsanto Hardness Tester”. An average of five observations in each batch was reported.¹⁷

Friability Test: Tablet hardness is not an absolute indicator of strength since some formulation when compressed into very hard tablet tends to “cap” on attrition, losing their crown portions. Therefore, another measure of a tablet’s strength is its friability, is measured. Friability of different batch was measured in “Roche friabilator”. 10 pre-weighted tablets of each batch were rotated at 25 rpm for 100 revolutions. The tablets were dusted and re-weighted and percentage of weight loss during test was calculated and reported in percentage.¹⁷

Disintegration Test: For absorption through oral route the tablet must break to become soluble in body fluid. This step of breaking of tablet in solution is called disintegration. Disintegration is defined as “that state in which no residue of the tablet or capsule remain on the screen of apparatus or if a residue remain it consist of fragments of insoluble coating of tablet or of the capsule shell or will the soft mass with no palpable core. If disc has been used with capsules any residue remain on the lower surface of the discs consists only of fragment of shells.” For this test 6 tablets of each brand were placed in the standard Disintegration apparatus, which contains distilled water 37°C ±2 °C and time for complete disintegration of tablet was recorded.¹³

RESULT AND DISCUSSION

The crude drug material procured from herb supplier was found to be as per quality parameters stated in the individual monograph of drug in Indian Herbal Pharmacopoeia 2006 which were taken as standard for evaluation purpose. Results are shown in table no. 6 & 7.

Table 5: Quantitative Evaluation of Crude Drugs

Sr. No.	Parameter	Guggal		Sunth		Arand (roots)	
		Standard*	Observed	Standard*	Observed	Standard*	Observed
1.	Foreign matter	Not more than 05%	4.85%	-	-	-	-
2.	Ethanol soluble extractives	Not less than 21%	35.0%	Not less than 02%	3.5%	Not less than 0.3%	4.9%
3.	Water soluble extractive	Not less than 37%	37.0%	Not less than 10%	12.7%	Not less than 0.9%	9.8%
4.	Total Ash	Not more than 13%	10.0%	Not more than 06%	5.93%	Not more than 0.8%	8.0%
5.	Acid insoluble ash	Not more than 04%	2.9%	Not more than 1.5%	1.5%	Not more than 1.0%	1.0%

(* Indian Herbal Pharmacopoeia, IDMA, Mumbai, 2002)

Sr. No.	Parameter	Giloe		Gokhru		Punarnava	
		Standard*	Observed	Standard*	Observed	Standard*	Observed
1.	Foreign matter	Not more than 2.0%	1.7%	Not more than 2.0%	2.0%	Not more than 2.0%	1.5%
2.	Ethanol soluble extractives	Not less than 3.0%	4.6%	Not less than 1.5%	1.5%	Not less than 3.0%	3.3%
3.	Water soluble extractive	Not less than 11.0%	20.0%	Not less than 16%	18.9%	Not less than 10.0%	15.0%
4.	Total Ash	Not more than 11.0%	07.0%	Not more than 14%	11.0%	Not more than 13%	12.7%
5.	Acid insoluble ash	Not more than 2.0%	1.3%	Not more than 1.0%	1.0%	Not more than 4.0%	3.7%

(* Indian Herbal Pharmacopoeia, IDMA, Mumbai, 2002)

The crude drugs were converted into fine powder form and properly mixed together as per designed matrix. The prepared powder formulation (P1) found to have more bulk volume which leads to increases in dose and is not suitable for compression in a single tablet. So the reduction of dose was done by using some drugs as powder and other as aqueous extracts. The aqueous extract was absorbed on the powder and dried to prepare powder for tablet compression (P2).

From this Powder formulation P2 the granules was prepared using different binders i.e. Guggal, Sucrose solution, Gum Acacia and Starch solution and evaluated for their flow behavior. All the granules was found to have good flow behavior and adequate compressibility property (Table no.8).

Table 6: Evaluation of Granules

Sr. No.	Parameter	Observed Value			
		G1	G2	G3	G4
1.	Bulk Density	0.71	0.73	0.77	0.75
2.	Compressibility index	36.0	31.8	30.58	32.42
3.	Angle of repose	29.4	24.7	23.10	22.14

The result of granular evaluation shows that granules G3 and G4 are more suitable for tablet compression. The comparative results of granular property are represented in figure 1 to Figure3 which shows that the bulk density of granule G3 and G4 are up to the mark for tablet compression where as G1 have best angle of repose and compressibility index.

Figure 1: Comparative Bulk Density of Granules.

Figure 2: Comparative Angle of Repose of Granules.

Figure 3: Comparative Compressibility Index of Granules.

Tablets were compressed from the granules prepared in different batches (G1-G4) after mixing lubricant, talc and magnesium stearate and evaluated for quality parameters i.e. Weight variation, Hardness, Friability and Disintegration time (Table no. 9). The tablet with Granules G4 was found suitable for further studies.

Table 7: Evaluation of Tablet batches

Sr. No.	Parameter	Observed Value			
		G1	G2	G3	G4
1.	Weight variation	-1 to +1%	-1.5 to 1%	-1.5 to +1.5%	-1.2 to +1.6 %
3.	Hardness (kg/cm²)	2.7	3.2	3.8	5.0
3.	Friability (%)	2.0%	1.0%	0.8%	0.5%
4.	Disintegration time (sec.)	30	45	53	60

The comparative Hardness and Disintegration time of different tablet batch was shown in figure 4 and 5. The graph shows that G4 tablets are having maximum hardness among all batches where as G2 and G3 are suitable on the basis of disintegration studies.

Figure 4: Comparative Hardness of Different Tablet Batch.

Figure 5: Comparative Disintegration Time of Different Tablet Batch

CONCLUSION

In this study attempt was made to develop new polyherbal anti-arthritic formulation on scientific basis. The crude drugs were purchased from local herb supplier and qualitative & quantitative parameters were evaluated on laboratory scale for characterization of raw material. All the crude drugs are combined into suitable proportions as per designed formulation matrix to develop a single poly herbal anti-arthritic formulation (P1) by proper blending of raw drug and their extracts. Before development of solid dosage form the work was done on reduction in powder volume so that the dosage size can be reduced. For this the different Herbal ingredients were used in powder and extract forms. Extracts were adsorbed on powder one by one after carefully sun-drying which minimize the loss of active ingredient during the process. Finally the prepared powder was grinded to forms poly herbal formulation (P2). Drug extracts were prepared either through maceration or decoction. The powder P2 was used for further development of tablet dosage form.

Tablet dosage forms were developed in different batches ($G_1 - G_4$) by changing the nature of binding agents. Granules of each batch was prepared as per designed formula and evaluated for their flow behavior. First attempt was made to compress the tablet without using any additive because the guggal, used in extract form also act as binding agent, so granules were prepared from powder and mix with lubricating additive and finally compressed with help of cadmach rotary tablet press. But the problem of these tables was high friability (2%), which necessitates the use of other binding agent in the formulation. Then in second step granules G_2 were prepared by using sucrose solution as the binding agent, which also mask the odour and taste of the powder. The tablet evaluations were done for general appearance, weight variation, hardness, friability and disintegration time. Further for improving the binding property acacia was used as binding agent in granule G_3 , which reduces friability and enhance the

disintegration time. In last finally tablets G_4 were prepared by using most common binder i.e. starch paste which gave the required tablet properties for adequate stability. Hence the patient compliant formulation could be developed.

Further the studies are proposed for development of analytical method for dosage form evaluation (dissolution) through marker analysis on HPLC, HTPLC and in-vivo pharmacological evaluation for anti-arthritic potential of the formulation in laboratory animals & human volunteer. The final tablet dosage form (G_4) was provided to ayurvedic physicians for their in clinic use and assessment for therapeutic effectiveness of polyherbal formulation in tablet dosage form.

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Conflict of Interest: NIL

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