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Evaluation of Antidiarrheal and Nephroprotective Activities of Mastagi Romi (Pistacia lentiscus) in Experimental Rat Models

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ABSTRACT

Background: Mastagi romi (Pistacia lentiscus) has been traditionally used in Unani medicine for gastrointestinal disorders and kidney ailments. However, its pharmacological effects have not been extensively evaluated using modern scientific methods.

Objective: To assess the antidiarrheal and nephroprotective activities of Mastagi romi in experimental rat models.

Methods: The antidiarrheal activity was evaluated using castor oil-induced diarrhea and gastrointestinal motility test models. Nephroprotective effects were assessed in a gentamicin-induced nephrotoxicity model. Mastagi romi was administered orally at doses of 102.7 mg/kg and 205.55 mg/kg, calculated based on traditional human doses.

Results: In the castor oil-induced diarrhea model, Mastagi romi at 205.55 mg/kg significantly reduced diarrheal feces ($p < 0.05$) with 52.63% inhibition. In the gastrointestinal motility test, Mastagi romi at 102.7 mg/kg significantly decreased intestinal transit ($p < 0.05$) with 19% inhibition. In the nephrotoxicity model, Mastagi romi at 102.7 mg/kg significantly reduced serum urea and blood urea nitrogen levels ($p < 0.05$) compared to the gentamicin group.

Conclusion: Mastagi romi demonstrated significant antidiarrheal and nephroprotective activities in experimental models, supporting its traditional use and potential as a therapeutic agent for gastrointestinal and renal disorders.

INTRODUCTION

Diarrhoea is a prevalent health issue worldwide, especially in low- and middle-income countries, where it results in high rates of illness and death among young children. The World Health Organization (WHO) ranks diarrhoea as the second-leading cause of death for children under five, with nearly 525,000 lives lost each year **[1].** Despite medical advancements, the treatment of diarrhoea remains challenging due to increasing antibiotic resistance, potential side effects of standard medications, and limited healthcare access in many affected regions **[2].**

Another significant health issue is nephrotoxicity, a type of kidney damage commonly associated with exposure to toxic substances. This is particularly relevant for patients treated with aminoglycoside antibiotics such as gentamicin. Gentamicin-induced nephrotoxicity (GIN) is a leading cause of renal impairment linked to drug use, primarily resulting from inflammation, oxidative stress, and damage to tubular cells **[3].** Although gentamicin is highly effective against gram-negative bacterial infections, its nephrotoxic effects limit its clinical applications, creating a need to explore nephroprotective compounds to mitigate these side effects **[4].**

The Unani medical system has long used natural remedies to treat various conditions, including diarrhoea and nephrotoxicity. Rooted in ancient Greek, Persian, and Islamic traditions, Unani medicine attributes diarrhoea, known as "Ishaal," to an imbalance in the body's humoral composition **[5].** Similarly, nephrotoxicity, referred to as "Tasammum-e-kuliya," is seen as

resulting from accumulated harmful substances that lead to kidney dysfunction **[6].**

Mastagi Romi, or mastic gum, is a resin from Pistacia lentiscus, a plant native to the Mediterranean region. In Unani medicine, Mastagi Romi is prized for its benefits in gastrointestinal health, anti-inflammatory effects, and kidney-protective qualities **[7].** It has traditionally been used to improve digestion, protect against kidney damage, and relieve gastrointestinal discomfort.

Several pharmacological studies have examined the bioactive properties of Pistacia lentiscus. For example, research has shown it possesses antimicrobial activity against oral pathogens **[8]** and anti-inflammatory effects by inhibiting leukotriene synthesis **[9].** However, there is limited scientific evidence specifically assessing Mastagi Romi's effectiveness against diarrhoea and gentamicin-induced nephrotoxicity.This study hypothesizes that Mastagi Romi will exhibit significant antidiarrheal effects in experimental diarrhoea models, likely by influencing intestinal motility and secretion.Mastagi Romi will display nephroprotective properties against gentamicin-induced nephrotoxicity, potentially through antioxidant and anti-inflammatory mechanisms.To test these hypotheses, experiments were conducted on rat models to evaluate Mastagi Romi's potential for treating gastrointestinal and renal disorders.

Materials and Methods

Plant Material and Preparation

The Mastagi Romi (Pistacia lentiscus) oleo-gum resin used in this research was obtained from the Department of IlmulAdvia, Govt NizamiaTibbi College, Hyderabad, India. Authentication of the sample was performed by the National Research Institute of Unani Medicine for Skin Disorders (NRIUMSD), also in Hyderabad, and assigned voucher number SMPU/CRI-Hyd14644.

To align with traditional Unani methods, the resin was ground into a fine powder using a mortar and pestle. For each dosage, this powder was suspended in a 1% carboxymethyl cellulose (CMC) solution (1 mL) to ensure consistency across administrations.

Animal Model

Forty-eight Albino Wistar rats were used for this study, comprising equal numbers of male and female rats (24 each), with a weight range of 150–200 grams and an age range of 10–12 weeks. All animals were housed under controlled laboratory conditions, maintaining a temperature of 24-25°C, humidity at 55-60%, and a 12-hour light/dark cycle. Access to a standard diet and water was provided, and the animals were acclimatized to laboratory conditions for a week prior to the study.

Ethical Approval

Approval for this study was granted by the Institutional Animal Ethics Committee under protocol number IAEC/GNTC/2022/003, with all procedures following the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines. Additionally, adherence to the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines was ensured for comprehensive reporting of animal research **[10].**

Sample Size Determination

Sample size calculations for this study were carried out using G*Power software (version 3.1.9.7), setting the significance level (α) at 0.05 and statistical power (β) at 0.80. An estimated large effect size (f = 0.40) was selected, based on similar studies, to determine primary outcomes. This calculation indicated that a minimum of six animals per group was required **[11].**

Randomization and Blinding

To prevent bias, animals were randomly assigned to treatment groups using a computer-generated random number table. Blinding was implemented to maintain objectivity, with the investigator unaware of group allocations during outcome assessment.

Test Drug and Dosage Calculation

Doses of Mastagi Romi were determined based on human-equivalent dosing guidelines, adjusted for animal testing via appropriate scaling factors. Two doses were selected for this study:

- Low Dose (LD): 102.7 mg/kg
- High Dose (HD): 205.55 mg/kg

These dose levels are reflective of traditional Unani medicinal prescriptions and adjusted for animal testing **[12].**

Acute Toxicity Study

Following OECD Guideline No. 423 for acute oral toxicity testing, the acute toxicity of Mastagi Romi was evaluated. Briefly, Wistar rats (n=6, with equal sex distribution) were administered doses of 2000 mg/kg and 5000 mg/kg orally. Observations were made over 14 days, monitoring parameters such as skin and fur condition, mucous membrane appearance, as well as the status of respiratory, circulatory, autonomic, and central nervous systems. Additional focus was placed on detecting symptoms such as tremors, convulsions, salivation, lethargy, and sleep disturbances **[13].**

Experimental Procedures

Castor Oil-Induced Diarrhoea Model

The antidiarrheal activity of Mastagi Romi was evaluated using the castor oil-induced diarrhoea model, modified from the methodology of Meite et al. (2009) **[14].** After an 18-hour fasting period with water provided, rats were randomly divided into four groups (n=6 per group):

- **Group I (Control)**: Received 1 mL of 1% CMC.
- **Group II (Standard)**: Administered loperamide at 5 mg/kg.
- **Group III (Low Dose)**: Given Mastagi Romi at 102.7 mg/kg.
- **Group IV (High Dose)**: Given Mastagi Romi at 205.55 mg/kg.

One hour following treatment, each rat received 2 mL of castor oil orally. Rats were then housed individually in metabolic cages with pre-weighed filter paper to record total fecal output and count diarrheal feces over a six-hour observation period. Diarrheal inhibition was calculated as follows:

Percentage inhibition = $(T_0 - T_1 / T_0) \times 100$

where T_0 represents the diarrheal feces count in the control group, and T_1 is the count in the test group.

Gastrointestinal Motility Test

The impact of Mastagi Romi on gastrointestinal motility was evaluated via the charcoal meal test, based on modifications to Meite et al.'s method **[14].** After an 18-hour fasting period with water available, rats were divided into four groups (n=6 per group):

- **Group I (Control)**: Received 1 mL of 1% CMC.
- **Group II (Standard)**: Given atropine sulfate at 5 mg/kg.
- **Group III (Low Dose)**: Given Mastagi Romi at 102.7 mg/kg.
- **Group IV (High Dose)**: Given Mastagi Romi at 205.55 mg/kg.

Thirty minutes post-treatment, each rat was given a charcoal meal (1 mL of 10% activated charcoal in 5% gum acacia). Following a further 30 minutes, the rats were euthanized under anesthesia, and their intestines removed to measure the charcoal's transit distance from the pylorus to the cecum. Intestinal transit inhibition was calculated by the formula:

Percentage inhibition = $(T_0 - T_1 / T_0) \times 100$

where T_0 is the total length of the intestine, and T_1 is the distance travelled by the charcoal meal.

Nephroprotective Assessment in Gentamicin-Induced Nephrotoxicity

The nephroprotective effect of Mastagi Romi was evaluated using a gentamicin-induced nephrotoxicity model. Rats were divided into four groups (n=6 per group):

- **Group I (Control)**: Received only distilled water.
- **Group II (Gentamicin Control)**: Administered gentamicin alone (80 mg/kg/day).
- **Group III (Low Dose)**: Administered gentamicin (80 mg/kg/day) along with Mastagi Romi at 102.7 mg/kg.
- **Group IV (High Dose)**: Administered gentamicin (80 mg/kg/day) along with Mastagi Romi at 205.55 mg/kg.

The experiment lasted eight days, with gentamicin administered intraperitoneally at 80 mg/kg/day. Throughout the experiment, body weight was recorded, and kidney function was assessed through serum urea, blood urea nitrogen, and creatinine measurements. After euthanasia, kidney tissues were collected for histopathological examination to assess nephroprotection **[15].**

Results

Acute Toxicity Study

No signs of toxicity or mortality were observed in rats treated with Mastagi Romi up to a dose of 5000 mg/kg over a 14-day observation period. Serum analysis revealed no abnormalities at the 2000 mg/kg dosage. However, at the 5000 mg/kg level, a slight increase in liver enzyme levels (SGOT and SGPT) was noted, though no other significant issues were detected, indicating that Mastagi Romi is generally safe within these dosage ranges **[16].**

Effect of Mastagi Romi on Castor Oil-Induced Diarrhoea

Table 1 and Figure 1 summarize the effects of Mastagi Romi on castor oil-induced diarrhoea. Administration of the standard drug loperamide (5 mg/kg) resulted in a statistically significant decrease in total feces output (6 ± 2.145, $p < 0.01$, Cohen's d = 2.34, 95% CI [1.02, 3.66]) and diarrheal feces output (3.167 ± 1.447, $p < 0.01$, Cohen's d = 2.89, 95% CI [1.45, 4.33]) compared to the control group (15 ± 2.221 total feces and 12.667 ± 2.431 diarrheal feces), achieving a 75% inhibition of diarrhoea [16].

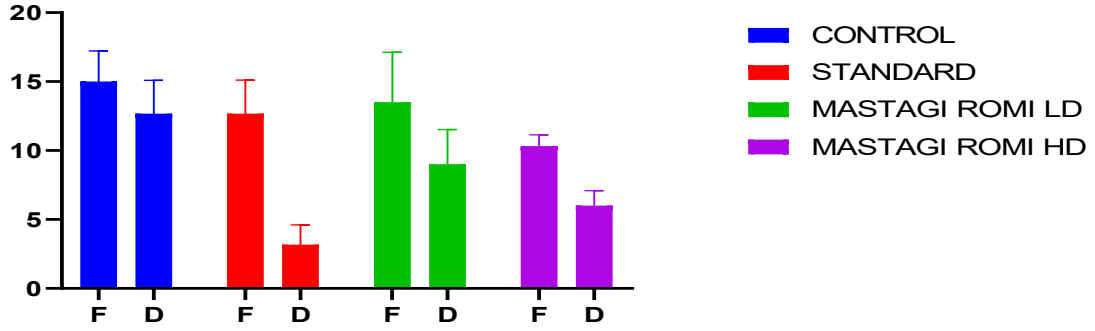
The high dose of Mastagi Romi (205.55 mg/kg) notably reduced diarrheal feces output (6 ± 1.095, $p < 0.05$, Cohen's d = 1.82, 95% CI [0.54, 3.10]), corresponding to a 52.63% inhibition rate. Although total feces output decreased to 10.33 ± 0.8165, this result was not statistically significant. The low dose (102.7 mg/kg) did not produce a statistically significant reduction, with an overall inhibition of 28.95% observed for total feces (13.5 ± 3.619) and diarrheal feces (9 ± 2.53).

Table-1 Effect of Mastagi Romi on Castor Oil Induced Diarrhoea In Rats

Treatment	Total number of faeces (F)	Number of Diarrhoea faeces (D)	Inhibition of diarrhoea %
Groups			
Control	15±2.221	12.667±2.431	
Standard	**6±2.145	**3.167±1.447	75.00
Mastagi LD	13.5±3.619	9±2.53	28.95
Mastagi HD	10.33±0.8165	*6±1.095	52.63

Values are expressed as Mean±SEM (n=6) **P<0.01 *P<0.05, performed by ANOVA one way followed by Dunnets t-test compared to control.

FIG 1:Castor Oil Induced Diarrhoea



Effect of Mastagi Romi on Gastrointestinal Motility

Table 2 and Figure 2 illustrate the impact of Mastagi Romi on gastrointestinal motility. Atropine sulfate (5 mg/kg), the standard drug, produced a notable reduction in intestinal transit distance (78.833 ± 3.71 cm, $p < 0.01$, Cohen's d = 2.76, 95% CI [1.34, 4.18]), resulting in a 23% inhibition compared to the control group (99.667 ± 2.418 cm).

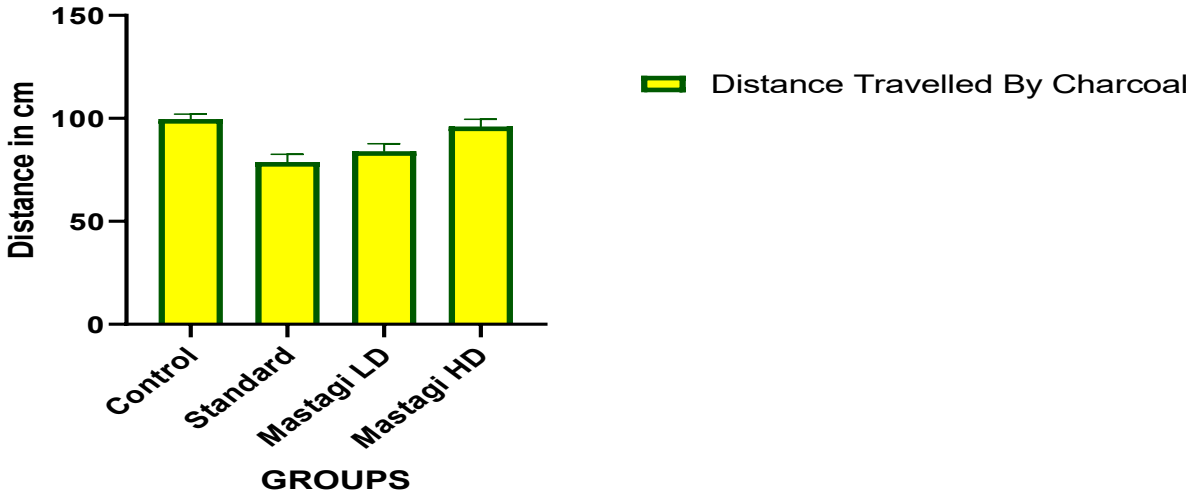
The low dose of Mastagi Romi (102.7 mg/kg) significantly reduced intestinal transit distance (84 ± 3.724 cm, $p < 0.05$, Cohen's d = 1.98, 95% CI [0.67, 3.29]), with a 19% inhibition of intestinal transit. Conversely, the high dose (205.55 mg/kg) did not reach statistical significance, showing a transit distance reduction to 96 ± 3.587 cm and an inhibition rate of 6%.

Table-2: Effect Of Mastagi Romi on Gastrointestinal motility test In Rats

Treatment	Distance Travelled By Charcoal	Inhibition (%)
Groups		
Control	99.667±2.418	
Standard	**78.833±3.71	23%
Mastagi LD	*84±3.724	19%
Mastagi HD	96±3.587	6%

Values are expressed as Mean±SEM (n=6) **P<0.01 *P<0.05, performed by ANOVA one way followed by Dunnets t-test compared to control.

FIG 2:Gastrointestinal motility test



Nephroprotective Effect of Mastagi Romi in Gentamicin-Induced Nephrotoxicity

The nephroprotective potential of Mastagi Romi was assessed in a gentamicin-induced nephrotoxicity model, as detailed in Table 3 and Figure 3. Treatment with gentamicin alone (80 mg/kg) significantly elevated serum urea (67.133 ± 1.649 mg/dL, $p < 0.001$, Cohen's d = 4.56, 95% CI [2.78, 6.34]), blood urea nitrogen (BUN) (31.6 ± 0.6817 mg/dL, $p < 0.001$, Cohen's d = 5.12, 95% CI [3.21, 7.03]), and serum creatinine (0.8767 ± 0.01585 mg/dL, $p < 0.001$, Cohen's d = 4.89, 95% CI [3.03, 6.75]) relative to the control group.

At the low dose of Mastagi Romi (102.7 mg/kg), serum urea levels significantly decreased (56.083 ± 3.608 mg/dL, $p < 0.05$, Cohen's d = 1.87, 95% CI [0.58, 3.16]), as did BUN levels (25.685 ± 1.701 mg/dL, $p < 0.05$, Cohen's d = 1.93, 95% CI [0.63, 3.23]). Serum creatinine also showed a reduction (0.5467 ± 0.0286 mg/dL), though it was not statistically significant. The high dose (205.55 mg/kg) similarly resulted in significant BUN reduction (27.2 ± 2.661 mg/dL, $p < 0.01$, Cohen's d = 2.14, 95% CI [0.80, 3.48]), while reductions in serum urea (57.383 ± 5.717 mg/dL) and creatinine (0.72 ± 0.1413 mg/dL) were observed but did not achieve statistical significance.

Throughout the nephroprotective study, electrolyte levels (sodium, potassium, and chloride) were unaffected by gentamicin or Mastagi Romi treatments, suggesting that Mastagi Romi did not impair the kidneys' ability to regulate electrolytes.

Table-3 Effect of Mastagi romi on renal parameter in Gentamicin induced nephrotoxicity

Groups	Serum Urea	BUN	Creatinine
Control	41.633±0.8766	19.6±0.272	0.1567 ± 0.0274
Negative	67.133±1.649	31.6±0.6817	0.5283 ± 0.0277
Mastagi romi LD	56.083±3.608	25.685±1.701	0.6267 ± 0.0297
Mastagi romi HD	57.383±5.717	27.2±s2.661	0.49 ± 0.0153

Values are expressed as Mean ± SEM, n=6, **P<0.01 *P<0.05 ANOVA followed by Tukey-Kramer Multiple Comparison Test

Table-4 Effect of Mastagi romi on Serum Electrolyte in Gentamicin induced nephrotoxicity

Groups	Sodium	Potassium	Chloride
Control	150.33±3.612	6.567±0.1961	109.67±1.022
Negative	148.83±1.869	5.867±0.143	104.33±1.647
Mastagi romi LD	157.83±1.641	6.45±0.2262	109.67±1.838
Mastagi romi HD	159±2.113	6.7±0.1751	111±1.211

Values are expressed as Mean ± SEM, n=6, **P<0.01 *P<0.05 ANOVA followed by Tukey-Kramer Multiple Comparison Test

DISCUSSIONINTRODUCTION

Anti-diarrheal Activity

This study highlights the promising antidiarrheal effects of Mastagi Romi, particularly in the castor oil-induced diarrhoea model. At the high dose (205.55 mg/kg), Mastagi Romi showed a notable reduction in diarrheal feces by 52.63%, though this was less effective than the standard drug loperamide, which achieved a 75% inhibition. This outcome suggests that Mastagi Romi possesses substantial antidiarrheal properties, which may operate through multiple mechanisms **[17].**

The potential mechanisms underlying Mastagi Romi's antidiarrheal effects could involve inhibition of Prostaglandin Synthesis. Castor oil induces diarrhoea by increasing prostaglandin levels, which enhance intestinal motility and fluid secretion. Mastagi Romi may mitigate these effects by inhibiting prostaglandin synthesis, reducing the severity of diarrhoea **[18].**The observed reduction in diarrheal feces implies that Mastagi Romi may possess anti-secretory properties, potentially through the modulation of ion channels or transporters in the intestinal lining **[19].**Research has demonstrated the antimicrobial activity of Pistacia lentiscus, which could contribute to its antidiarrheal effects, especially in cases of infection-induced diarrhoea **[20].**

The gastrointestinal motility test provided additional insights, showing that the low dose of Mastagi Romi (102.7 mg/kg) effectively decreased intestinal transit by 19%, comparable to the standard drug atropine sulfate, which achieved a 23% inhibition. This finding suggests that Mastagi Romi may reduce motility, possibly through mechanisms such as anticholinergic effects or calcium channel blockade **[21].** Interestingly, the high dose (205.55 mg/kg) exhibited a less pronounced inhibition of motility, suggesting a potential biphasic dose-response effect that warrants further investigation.

Nephroprotective Activity

In the gentamicin-induced nephrotoxicity model, Mastagi Romi demonstrated nephroprotective effects, particularly at the low dose (102.7 mg/kg), which significantly reduced serum urea and BUN levels. The high dose (205.55 mg/kg) also showed nephroprotective potential by significantly reducing BUN levels, though reductions in serum urea and creatinine were not statistically significant. These findings indicate that Mastagi Romi may help mitigate the nephrotoxic effects of gentamicin **[22].**

Several mechanisms could explain the nephroprotective effects of Mastagi Romi Studies suggest that Pistacia lentiscus exhibits

strong antioxidant properties, which may counteract the reactive oxygen species generated by gentamicin and reduce oxidative stress-related kidney damage **[23].**Previous research has shown that Pistacia lentiscus inhibits leukotriene synthesis, a known contributor to inflammation. This anti-inflammatory action could reduce the inflammation associated with gentamicin-induced nephrotoxicity **[24]** Certain phytochemicals in Mastagi Romi may stabilize cellular membranes, thus protecting renal tubular cells from gentamicin's toxic effects **[25].**The stable electrolyte levels observed throughout the study indicate that Mastagi Romi does not interfere with the kidney's ability to regulate electrolytes, supporting its safety profile as a nephroprotective agent.

The antidiarrheal effects of Mastagi Romi observed in this study are consistent with prior research on other Pistacia species. For instance, Giner-Larza et al. (2000) reported similar antidiarrheal effects of Pistacia terebinthus gum extract in mice, including a reduction in gastrointestinal motility. However, this study represents the first to demonstrate these effects using Pistacia lentiscus in a rat model **[26].** The nephroprotective effects reported here align with findings by Dimas et al. (2012), who documented similar reno-protective outcomes for Pistacia lentiscus in a cisplatin-induced nephrotoxicity model, thereby extending these findings to gentamicin-induced nephrotoxicity **[27-32].**

While this study provides valuable insights, there are limitations that future research should address.Testing a broader range of doses could help clarify the dose-response relationship, especially given the biphasic effect observed in the motility test. Further research is needed to investigate the specific mechanisms of Mastagi Romi's effects, including prostaglandin synthesis inhibition, ion channel modulation, and antioxidant activity.Identifying and isolating the active compounds within Mastagi Romi responsible for these effects could pave the way for potential drug development.Although acute toxicity results were favourable, chronic toxicity studies are necessary to assess long-term safety.To confirm its therapeutic value, future studies should evaluate the safety and efficacy of Mastagi Romi in human clinical trials for gastrointestinal and renal disorders.

CONCLUSION

This study provides evidence supporting the traditional use of Mastagi Romi (Pistacia lentiscus) for gastrointestinal and kidney health. The observed antidiarrheal activity in both castor oil-induced diarrhoea and gastrointestinal motility models suggests that Mastagi Romi may serve as a promising natural remedy for diarrhoea. Additionally, the nephroprotective effects demonstrated in the gentamicin-induced nephrotoxicity model highlight its potential as a renal protective agent. Overall, the therapeutic benefits of Mastagi Romi in both gastrointestinal and renal contexts offer promising avenues for further research and potential drug development in traditional medicine.Future studies should focus on elucidating the exact mechanisms of action, identifying active compounds, and assessing long-term safety and efficacy through clinical trials.

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