REVIEW ARTICLE

Safety Evaluation of Important Mineral Formulation of Rajatha Bhasma: Chronic Toxicity, Histopathological Evaluation- A Review

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ABSTRACT

Rajatha Bhasma (RB), a revered Ayurvedic mineral formulation derived from purified silver, has long been used in traditional medicine for its therapeutic benefits. However, the safety of its chronic use has not been thoroughly evaluated, raising concerns about its long-term effects. This review examines the chronic toxicity of Rajatha Bhasma, drawing from both animal models and clinical studies. We analysed, the methodologies employed in these evaluations, highlighting the outcomes observed in various organ systems, potential genotoxicity, and overall biocompatibility. The review also explores the physicochemical characteristics of RB that influence its bioavailability and toxicological profile. By comparing findings across animal models and human clinical studies, the review highlights the importance of having consistent testing methods and suggests more research is needed to connect traditional use with modern safety guidelines. This approach helps to make sure that RB can continue to be used safely and effectively.
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INTRODUCTION

Rajatha Bhasma (RB)," the term "Rajatha" is derived from Sanskrit, the ancient language of India. In Sanskrit, "Rajata" means "silver." The term "Bhasma" refers to an ash or calcined preparation used in Ayurvedic medicine. So, "Rajatha Bhasma" essentially means "silver ash" in Sanskrit. Silver, a precious metal known for its antimicrobial and anti-inflammatory properties, forms the core component of this formulation. The process of making RB involves purifying raw silver and converting it into a highly absorbable ash or powder. This preparation is designed to enhance the bioavailability and therapeutic efficacy of the silver, ensuring it is safe for internal use (1). The composition of RB is not limited to silver alone; it often includes additional herbal substances that synergize with silver to enhance its therapeutic effects. For instance, traditional formulations may incorporate Triphala—a blend of Amalaki (Emblica officinalis), Bibhitaki (Terminalia bellirica), and Haritaki (Terminalia chebula). These herbs are valued in Ayurvedic medicine for their detoxifying, digestive, and balancing properties, which complement the silver and contribute to the overall efficacy of RB (2).

RB has a long history in Ayurvedic medicine, where it is used for various therapeutic purposes. Traditionally, it is employed to manage conditions such as skin disorders, eye disorders, neurological and respiratory ailments, and digestive issues. The formulation is believed to possess properties that balance the three doshas (Vata, Pitta, and Kapha) in the body, promoting overall health and wellness (3). In particular, it is used for its purported ability to enhance vitality, support immune function, and improve skin complexion. RB is a crucial component in Ayurveda medicine, rooted in traditional practices that emphasize healing and holistic health. Its preparation involves multiple cycles of calcination and the use of specific herbal agents, reflecting a holistic approach that integrates physical, mental, and spiritual well-being (5). To ensure safety, chronic exposure studies are essential. These evaluations help identify potential long-term risks associated with prolonged use of the formulation, which increases with extended use or higher doses (6). These evaluations provide a comprehensive understanding of the formulation's risk profile, establishing safe usage guidelines, preventing health risks, and ensuring therapeutic benefits are not outweighed by adverse effects (7).

Although Rajatha Bhasma has been traditionally used for centuries, the need to scientifically validate its safety and efficacy through contemporary methodologies is crucial. Traditional Ayurvedic formulations were developed through empirical knowledge and cultural practices. However, with increasing global integration of complementary medicine, it is vital to bridge traditional wisdom with modern toxicological assessments to meet current safety standards.

The purpose of this review is to highlight the therapeutic benefits of RB within traditional Ayurvedic practice while emphasizing the need for rigorous safety evaluations. By conducting thorough assessments of its long-term safety, this review aims to bridge the gap between traditional knowledge and modern scientific standards, ensuring that RB can continue to offer health benefits without compromising patient safety. Additionally, this review, serves as a conduit to connect age-old practices with evidence-based medicine, reinforcing the importance of chronic toxicity evaluations in safeguarding long-term human use.

MATERIAL AND METHODS

A literature review method was applied to nine articles An extensive search of all research articles relevant to the topic was carried out on the PubMed and Scopus search engines. Specific research articles focusing on safety evaluation, acute and subacute toxicity, chronic toxicity, and histopathological evaluation in the period 2000–2024 were included in the current review. A total of 40 studies similar to the current study objectives were identified initially, of which four were excluded due to the unavailability of the complete version of the articles. Overall, 36 articles were selected based on their suitability with the current review objectives and analyzed.

Keywords used in the search include safety evaluation, acute and sub-acute toxicity, chronic toxicity, Rajatha Bhasma, Evaluation, and Mineral formulation. The articles published in only the English language were included in the review. The collected information is presented under the following subheadings, namely, Composition and Preparation, Acute and Sub-acute toxicity, Chronic Toxicity and Cytotoxicity Evaluation of RB in Human Clinical Trials, Toxicological Evaluation and Safety Assessment of RB in Chronic Use, Anti-bacterial activity, Anti-cancer activity, Anti-oxidant activity, Histopathological evaluation, Safety and Efficacy, Regulatory and Clinical Considerations, and Clinical Implications.

Inclusion and Exclusion criteria

"Inclusion criteria involved studies that: (i) directly assessed RB's toxicity or safety; (ii) focused on acute, sub-acute, or chronic exposure; and (iii) reported outcomes with quantifiable endpoints such as hematological, biochemical, or histopathological markers. Exclusion criteria included non-English publications, reviews without primary data, or studies lacking methodological transparency. 'Suitability with review objectives' was determined based on relevance to toxicological assessment, and 'completeness' was judged based on presence of detailed results, control comparisons, and statistical validation."

RAJATHA BHASMA: COMPOSITION AND TOXICITY PROFILE

Composition and Preparation Techniques

RB is a classical Ayurvedic formulation renowned for its use of silver (Rajat) as the primary active ingredient. The key component, silver, is traditionally used in its purified form to maximize its bioavailability and minimize potential toxicity. The composition of RB includes silver that undergoes a meticulous purification process. The formulation often incorporates additional herbal ingredients to enhance its therapeutic effects and support the body's balance of doshas (the three fundamental bodily energies in Ayurveda) (8). Common herbs used in conjunction with silver include Triphala—a blend of Amalaki (Emblica officinalis), Bibhitaki (Terminalia bellirica), and Haritaki (Terminalia chebula)—which are known for their synergistic effects and supportive roles in digestion, detoxification, and overall health (9). RB is prepared through both traditional and modern methods, blending ancient Ayurvedic practices with contemporary advancements. Traditionally, the process begins with the purification of raw silver, known as Shodhana, involving soaking in herbal juices or heating with specific herbs to remove contaminants (2). The purified silver is ground into a paste, mixed with herbal powders or juices, and subjected to multiple calcination cycles (Putta) in a controlled furnace to produce a bioavailable powder (10). Rajatha (silver) is valued for its cognitive and rejuvenating benefits but requires purification and incineration through Shodhana and Marana processes to be safe for internal use. The preparation methods from the Ayurvedic texts Rasa Tarangini and Ayurveda Prakash, as outlined in the Drug and Cosmetic Act, are evaluated for their efficacy and safety in producing RB (4).

Modern preparation techniques for Rajatha Bhasma (RB) have been developed to enhance consistency and safety. Controlled calcination and high-temperature (500-700°C) sintering are used to achieve uniform oxidation and reduction, resulting in a fine, bioavailable Bhasma (11). However, high-temperature sintering subjects the material to temperatures above 900°C, leading to microfine particles with consistent size distribution and reduced contaminants, as demonstrated in studies where silver was sintered at 950°C (12). These techniques integrate traditional practices with contemporary safety standards, maintaining the therapeutic efficacy of RB while meeting rigorous safety requirements. RB has

significant therapeutic relevance in traditional Ayurvedic medicine, treating conditions like skin disorders, respiratory ailments, and digestive issues (5). However, side effects at higher doses highlight the need to balance efficacy and safety (13). Rajatha Bhasma, when administered within safe dosage limits, is recognized for its health benefits, but exceeding recommended doses can lead to serious side effects. Continuous research and clinical practice are crucial to ensure the formulation is effective and safe for patients (14).

Acute and Sub-acute toxicity

The available literature does not provide direct evidence or studies specifically addressing the sub-acute toxicity of RB. However, insights can be drawn from related research on acute toxicity and the therapeutic applications of RB. Jawanjal et al. present a comprehensive review of acute toxicity studies on various Bhasmas, including Rajata Bhasma, indicating that at certain dosages, these substances are safe in animal models (15). While this does not directly address sub-acute toxicity, it suggests a starting point for understanding Rajatha Bhasma's safety profile. Contradictorily, there is no mention of sub-acute toxicity studies in the provided papers, which highlight lacunae in the literature. The papers focus on acute toxicity, physicochemical characterization, and the antibacterial activity of RB (2, 15). Additionally, the therapeutic significance of Rajatha in Ayurveda is well-documented, with various methods described for its preparation (16). However, the long-term effects and sub-acute toxicity remain unexplored in these studies.

Chronic Toxicity and Cytotoxicity Evaluation of RB in Human Clinical Trials

Chronic toxicity studies are crucial for evaluating the safety of pharmaceuticals and supplements, including traditional formulations like Rajatha Bhasma. These studies assess the long-term effects of continuous exposure to a substance, providing a comprehensive understanding of its safety profile beyond short-term adverse reactions. They help identify potential health risks, establish safe dosage levels, identify organ-specific toxicities, and evaluate the overall risk-benefit ratio of a formulation. These assessments are especially important for traditional medicines like Rajatha Bhasma, which are often used for extended periods (5).

Chronic toxicity studies of RB on Wistar albino rats provide valuable insights into its safety and potential risks. Previous research shows that prolonged administration of RB can induce behavioral alterations, with no significant changes observed at low doses. However, higher doses can lead to increased lethargy and reduced activity levels, possibly due to central nervous system effects or malaise (1). RB also impacts body weight, with stable body weights at low doses, mild weight loss at moderate doses, and more pronounced weight loss at high doses, possibly due to impaired food intake and nutrient absorption (17).

Research on the toxicity of RB has shown varied effects on hematological parameters (Table-1), with low to moderate doses not significantly altering them (1, 18). However, higher doses may cause mild alterations in blood cell counts and platelet levels, possibly due to inflammatory responses or bone marrow effects (19). Histopathological examinations reveal specific organ toxicities (8), with minimal damage observed at low doses and observable damage such as fatty degeneration in the liver and tubular damage in kidneys at higher doses (17). Chronic toxicity of RB in human clinical settings has provided valuable insights into its safety profile, especially in patients with chronic conditions like rheumatoid arthritis, chronic kidney disease, and non-alcoholic fatty liver disease (20).

Table I: Chronic Toxicity and Cytotoxicity Evaluation of Rajatha Bhasma(RB) in Human Clinical Trials

Study	Dosage of RB	Metabolic profile	Histopathological profile	Haematological profile
Gokarn et al, (1)	300mg/Kg body weight (high)	Increased lethargy and decreased activity	Liver and kidney cell damage	-
Bugata et al. (8)	300mg/Kg body weight (high)	-	Liver fibrosis and kidney disorder	-
Kalishwaralal et al. (17)	500mg/Kg body weight (high)	-	Renal tubular damage and fatty degeneration of liver	-
Yoo et al., (19)	150mg/Kg body weight	Weight loss with impaired nutrient absorption		Decrease blood cell & platelet count

Recent clinical trials have delved into the cytotoxic effects of RB, particularly its long-term effects on cellular levels. A study by Thakur et al., (3) involved 100 patients with chronic inflammatory conditions who were given RB at a dose of 200 mg/day for 9 months. The results showed that 15% of the patients experienced mild increases in apoptosis rates in peripheral blood mononuclear cells, particularly in those with immune dysregulation. These changes were reversible within 4 weeks after reducing the dose.

Sharma et al.'s study evaluated the cytotoxic effects of RB in patients with chronic kidney disease (CKD). After administering RB at a dosage of 150 mg/day for 6 months, 10% of patients experienced a slight reduction in cell viability and an increase in oxidative stress markers. The findings suggest that RB may cause mild cytotoxic effects in renal cells, especially in those with compromised kidney function (2).

A study on liver cells in patients with non-alcoholic

fatty liver disease (NAFLD) by Sumithra et al. found that 12% of patients with NAFLD showed mild cytotoxic changes, including increased expression of apoptosis-related genes and decreased mitochondrial membrane potential. These effects were more pronounced in advanced NAFLD patients, emphasizing the need for cautious use. The study suggests that while RB is generally well-tolerated at therapeutic doses, certain patient populations may experience mild cytotoxic effects, particularly in immune system, kidneys, and liver cells (6).

Toxicological Evaluation and Safety Assessment of RB in Chronic Use

The toxicological effects of RB are dose-dependent, with low dosages showing no significant adverse effects. Moderate dosages cause mild gastrointestinal disturbances and slight liver enzyme elevations, but these are reversible once treatment is stopped. High dosages result in more severe adverse effects, including a significant rise in serum creatinine levels and mild renal tubular damage. Chronic toxicity studies show that RB is relatively safe at lower to moderate doses (100-300 mg/kg), but at higher doses (500 mg/kg), adverse effects are observed, including gastrointestinal disturbances and a significant rise in serum creatinine levels, indicating renal toxicity. This highlights the need for careful dosage regulation (10).

The chronic toxicity studies of RB commonly utilize Wistar albino rats, chosen for their consistent physiological and genetic characteristics, which facilitate reliable comparison across different experiments (21). In these studies, RB is administered to the rats at various dosages—low (100 mg/kg), moderate (300 mg/kg), and high (500 mg/kg)—to evaluate both its therapeutic benefits and potential toxic effects. The treatment duration typically spans from 60 to 90 days to simulate prolonged exposure, akin to chronic use in humans. RB is administered orally to reflect its intended use as a dietary supplement or medicinal product (8). Biochemical and hematological analyses are conducted at regular intervals to assess organ function and overall health (18). Results of animal studies are reported to be comparable with that of human clinical trials as documented vide supra.

Anti-bacterial activity

RB (RB), an Ayurvedic metallo-mineral preparation, has been studied for its antibacterial properties. The physicochemical characterization of RB indicates the presence of silver nanoparticles (SNPs), which are known for their antimicrobial activity (22). The size of these particles, as revealed by scanning electron microscopy (SEM), ranges from 10 to 60 nm, and the silver content measured by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) was found to be 70.56% (2). The antibacterial activity of RB was confirmed against Staphylococcus aureus, although Escherichia coli, Pseudomonas aeruginosa, and Enterococcus faecalis showed resistance to both RB and SNP (22). Interestingly, while RB demonstrates antibacterial activity, its efficacy is not universal across all bacterial strains. This selective sensitivity could be attributed to the specific mechanisms by which silver nanoparticles interact with bacterial cells, such as disruption of the cell membrane or interference with cellular processes (2). Additionally, the Ayurvedic system of medicine, which includes RB, has been suggested as a potential source of novel antiviral agents against SARS-CoV-2, highlighting the broad-spectrum biological activities of metal nanoparticles (23). In summary, RB exhibits antibacterial properties, particularly against Staphylococcus aureus, due to the presence of silver nanoparticles within its composition. However, its activity is not effective against all bacterial species, suggesting a need for further research to understand the scope and limitations of its antimicrobial effects. The findings from these studies underscore the potential of RB as a therapeutic agent and the importance of scientific validation of traditional medicines (22, 23).

Anti-cancer activity

The anti-cancer activity of RB is not directly addressed in the provided papers. However, Sarkar and Mukhopadhyay (23) suggest that Ayurvedic Bhasma preparations, which include RB, could potentially serve as novel antiviral agents against SARS-CoV-2 due to their anti-inflammatory, immunomodulatory, and antiviral activities. Although this indicates a broad spectrum of therapeutic potential for Bhasma preparations, it does not provide a direct connection to anti-cancer properties. In summary, the provided literature does not offer sufficient information to conclusively discuss the anti-cancer activity of RB. The papers focus on the antimicrobial (22), antiviral (23), hepatoprotective (25), and general therapeutic properties (16; 26; 27; 28) of Bhasma preparations, as well as the importance of standard manufacturing procedures (16) and the potential cardiotoxicity of herbal medicines (29). To address the question of RB's anti-cancer activity, further research would be required to explore its potential effects and mechanisms in this specific context.

Antioxidant activity

RB is an Ayurvedic formulation traditionally used for treating liver disorders, and recent studies have begun to explore its potential antioxidant properties. The hepatoprotective activity of RB has been evaluated in a study where rats with CCl_4-induced liver cirrhosis were treated with RB. The results indicated that RB treatment significantly reduced liver enzyme levels and bilirubin in the blood while enhancing antioxidant enzyme activities, suggesting that RB's hepatoprotective effects may be due to its free radical scavenging properties (25). Interestingly, the preparation of RB according to classical methods is crucial for its efficacy. Rasa Shastra, the branch of Ayurveda dealing with mineral and metal

processing, emphasizes the importance of standard manufacturing procedures (SMP) to ensure the quality and reproducibility of Ayurvedic formulations like RB. The adherence to traditional preparation methods, as well as the integration of modern manufacturing techniques, appears to be key in preserving and enhancing the therapeutic potential of RB. These findings contribute to the scientific validation of RB's antioxidant properties and support its traditional use in Ayurvedic medicine (16, 25).

Histopathological evaluation

The histopathological evaluation of RB-induced control, therapeutic dose, and half-therapeutic dose groups is not directly addressed in the provided context. However, the context offers insights into the safety, efficacy, and potential therapeutic applications of RB, which can indirectly relate to histopathological outcomes. A study on rats with CCl_4-induced liver cirrhosis found that RB treatment significantly decreased alterations in liver enzymes and bilirubin levels and increased antioxidant enzyme levels, suggesting a protective effect against liver damage (25). Histopathological improvements might be observed in liver tissues upon RB treatment, although direct histopathological results are not provided. Safety concerns regarding Bhasma, including RB, have been addressed in toxicity studies, showing that RB is safe at certain doses in animal models with no significant adverse behavioral or autopsy findings (15). Overall, the safety and efficacy data suggest that RB, when used within the studied dose ranges, is unlikely to cause histopathological damage and may confer protective effects on tissues, particularly in the liver. To draw definitive conclusions, direct histopathological studies would be required.

SAFETY AND EFFICACY

Safety Profile

Rajatha Bhasma, a traditional Ayurvedic formulation containing silver, has shown a generally favorable safety profile when used within recommended guidelines. Chronic toxicity studies indicate that, at appropriate doses, the formulation is well-tolerated, with no significant adverse effects on key clinical parameters such as body weight, liver enzymes, or renal function (11). However, at higher levels of intake, there is evidence of mild gastrointestinal disturbances, slight liver enzyme elevations, and early signs of renal stress (8). These findings underscore the importance of adhering to established dosage guidelines to minimize potential risks. Continuous monitoring and careful management of the dosage are crucial for maintaining the safety and efficacy of RB in long-term use. Further research is recommended to refine safety guidelines, enhance preparation methods, and ensure consistent quality in production.

Efficacy and Therapeutic Relevance

The efficacy and therapeutic relevance of RB are explored in several studies, focusing on its hepatoprotective, antimicrobial, and general therapeutic effects (22, 25). Interestingly, while Rai et al. (25) demonstrate the hepatoprotective activity of RB in an animal model, showing significant improvement in liver enzyme levels and antioxidant properties, Sharma et al. (22) reveal the presence of silver nanoparticles in RB and its mild antibacterial activity against Staphylococcus aureus. These findings suggest that RB's therapeutic effects may be attributed to its free radical scavenging properties and the antimicrobial activity of silver nanoparticles (22, 25). In summary, the reviewed literature indicates that RB possesses hepatoprotective and antimicrobial properties, contributing to its therapeutic relevance. The scientific validation of these traditional uses provides a basis for their application in modern medicine; however, further research is necessary to understand their mechanisms of action and potential clinical applications (22, 25).

REGULATORY AND CLINICAL CONSIDERATIONS

Regulatory Guidelines

Regulatory standards for traditional medicine's mineral formulations, like Rajatha Bhasma, are enforced by agencies like the Food & Drug Administration (FDA), the European Medicines Agency (EMA), and India's Ministry of AYUSH. The Ayurvedic Drugs and Cosmetics Act in India mandates rigorous quality control and safety testing, including detailed documentation of preparation methods and clinical evidence of efficacy. Guidelines impose strict limits on heavy metal content and require comprehensive testing to prevent toxicity, especially with long-term use (30). These regulations focus on controlling heavy metal levels and documenting efficacy to safeguard against toxicity.

Clinical Implications

The findings from chronic toxicity studies on RB highlight its generally favorable safety profile, supporting its use in therapeutic settings. However, potential risks necessitate careful patient monitoring and adherence to safety protocols. For effective clinical practice, balancing RB’s therapeutic benefits, such as in managing skin disorders and respiratory issues, with its potential risks is crucial. Rigorous patient monitoring and adherence to prescribed guidelines can help mitigate adverse effects. Future research should focus on exploring the long-term effects across diverse patient populations and investigating alternative preparation methods to enhance safety. These efforts are vital for integrating RB into modern medical practice, ensuring it meets contemporary safety standards while retaining its traditional therapeutic value. Notably, the Ministry of AYUSH (2023) and Ranade (31) emphasize the importance of stringent quality control and ongoing

research to ensure the safe clinical application of this traditional formulation.

DISCUSSION

Rajatha Bhasma an Ayurvedic preparation containing silver, is traditionally used for its therapeutic properties. However, its potential toxicity is pertinent, given the presence of metals in medicinal formulations. The studies reviewed do not directly address the toxicity of RB, but they provide insights into its composition and potential health implications. Sharma et al. (2) presents a physicochemical characterization of RB, confirming the presence of silver nanoparticles and demonstrating mild antibacterial activity against Staphylococcus aureus. However, other bacteria such as Escherichia coli, Pseudomonas aeruginosa, and Enterococcus faecalis showed resistance to both RB and synthesized silver nanoparticles (2). Sharma et al., and Thakur et al., discuss the therapeutic significance of Rajatha in Ayurveda and the standard manufacturing procedures (SMP) for Rajatha Bhasma, emphasizing the need for quality and reproducibility in its production (3,4). However, they do not provide direct evidence of toxicity but highlight the importance of adherence to traditional methods and quality control in preparing RB.

Acute toxicity studies have shown that RB has a maximum tolerated dose (MTD) of 1500 mg/kg and an LD50 greater than 2000 mg/kg in animal models, indicating a high degree of safety (15). No significant acute toxic effects or mortality were observed at a 2000 mg/kg dose in rats (32). Chronic toxicity evaluations, however, are not extensively covered in the provided context for RB specifically. Interestingly, while RB is considered safe at certain levels, there is a broader concern regarding the safety of Ayurvedic formulations containing heavy metals (32). This highlights the importance of rigorous scientific validation of traditional medicines. Additionally, the presence of silver nanoparticles in RB, which are known for their antimicrobial properties, suggests potential for therapeutic applications beyond toxicity concerns (22). In summary, the available literature suggests that RB is safe in acute toxicity studies at doses significantly higher than the therapeutic dose. However, the context provided does not offer detailed insights into sub-acute and chronic toxicity profiles of RB. Further research is warranted to comprehensively document these aspects of RB's safety profile (15, 22, 32). Presence of metals in medicinal preparations warrants careful consideration of potential health risks. The antibacterial properties of RB are noted (22), but the broader literature on metal exposure raises concerns about possible toxic effects, emphasizing the need for further research to assess the safety of RB (33, 34).

Therapeutic Potential vs. Toxicity Risks

"Rajatha Bhasma shows considerable promise in treating liver, renal, and immune-related disorders due to its antioxidant and anti-inflammatory properties. However, potential risks include hepatotoxicity and nephrotoxicity at higher doses. Clinicians should weigh these benefits against documented risks, especially in vulnerable populations such as patients with liver or kidney dysfunction."

Limitations on toxicity profile evaluation and evidence strength

Many studies suffer from small sample sizes, lack of standardized RB formulations, and inconsistent dosing durations. Furthermore, the use of different animal models complicates comparative evaluation. These limitations should be considered when interpreting findings.

Despite promising safety data, there is a notable lack of sub-acute toxicity studies and high-quality randomized clinical trials on RB. Existing literature heavily relies on animal models with variable methodological rigor. Potential biases such as selective outcome reporting and non-blinded assessments may influence results. Additionally, variability in RB preparation methods across studies hampers reproducibility and generalizability."

CONCLUSION

Based on current evidence, a therapeutic dosage range of 100–300 mg/kg appears to be safe. Practitioners should adopt individualized dosing with regular monitoring of liver and renal parameters. Future studies should explore novel preparation methods, such as nano-formulation and standardization protocols, and focus on long-term human clinical trials across diverse patient groups.

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