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REVIEW ARTICLE OPEN ACCESS

Integrated Perioperative Strategies in Infertility Management: Antisepsis, Oral Health Optimisation, and Enzymatic Therapy as Modulators of Inflammation with Potential Implications for ART Outcomes

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Abstract
Background: This narrative review examines three perioperative interventions, chlorhexidine antisepsis, oral health optimisation, and trypsin-chymotrypsin enzymatic therapy, and their potential influence on inflammatory reactions relevant to reproductive outcomes.
Main Body: A narrative literature search was conducted using major databases (PubMed, Scopus, Web of Science) to identify studies on perioperative infection control, periodontal inflammation, and enzymatic modulation of postoperative healing.
Chlorhexidine antisepsis may reduce microbial contamination and postoperative inflammatory cytokine activation. Oral health optimisation can lower systemic inflammation markers, including C-reactive protein (CRP) and interleukin-6 (IL-6). Enzymatic therapy has been associated with faster postoperative recovery and reduced tissue oedema. Although most existing literature evaluates inflammatory biomarkers and general postoperative outcomes rather than direct assisted reproductive technology (ART) outcomes, several studies suggest that improved inflammation management may foster a better endometrial environment for implantation.
Conclusion:
Current evidence indicates that perioperative interventions targeting systemic inflammation could help create physiological states more favourable to ART success. However, direct clinical evidence linking these combined strategies to improved implantation or live birth rates remains limited. Prospective clinical trials are needed to determine the impact of such interventions on reproductive outcomes.

Keywords: infertility, perioperative care, chlorhexidine, oral inflammation, enzymatic therapy, assisted reproductive technology, systemic cytokines.

Background

The worldwide health issue of infertility affects approximately 15% of couples attempting to conceive, and its medical implications extend beyond purely hormonal and anatomical factors (1). The success rate of assisted reproductive

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technologies (ART), including in-vitro fertilisation, depends strongly on biological conditions during implantation and early pregnancy, which may be influenced by systemic and perioperative factors (2). Increasing evidence suggests that low-grade systemic inflammation, postoperative infections, and delayed tissue recovery may represent hidden barriers to successful ART outcomes, making perioperative optimisation an important consideration for fertility care providers (3, 4).

Past research has indicated that postoperative inflammatory reactions with increased concentrations of C-reactive protein (CRP) and interleukin-6 (IL-6) can have adverse effects on the feasibility of implantation and pregnancy during ART cycles (5). Thus, the possibility of using the strategies that minimise systemic inflammation and stress on surgical tissue could help to achieve better reproductive conditions.

Chlorhexidine antisepsis is commonly perceived as one of the most effective antimicrobial interventions when applied as a method of postoperative infection reduction and surgical recovery enhancement in gynecologic surgery (6). On the same note, there is growing evidence that oral health and periodontal disease can lead to systemic inflammatory activation, which can inhibit endometrial receptivity and finally lower the success rate of ART treatments (7).

Moreover, the enzymatic trypsin-chymotrypsin proteolytic therapy has also been mentioned to decrease postoperative swelling, improve tissue healing, and shorten the recovery period after surgery (8). The quicker postoperative recovery can be earlier, and under more physiologically favourable circumstances, which will enable patients to start ART cycles. Clinical findings also indicate that patients who receive ART and who have not achieved oral health, adequate antiseptic control or slow wound healing have lower pregnancy outcomes despite having the best embryo (9).

Therefore, incorporating antiseptic measures, optimisation of oral health, and enzymatic anti-inflammatory care could help to establish the situation in the perioperative environment that facilitates surgery recovery, as well as reproductive success. Here, the current evidence on the topic of chlorhexidine antisepsis, oral inflammatory status, and enzymatic therapy is assessed in terms of postoperative recovery and its possible implications on the outcomes of ART.

Objectives

The research evaluates three surgical methods which combine chlorhexidine antisepsis with oral health enhancement and trypsin–chymotrypsin enzymatic treatment to determine their effects on postoperative recovery and Assisted Reproductive Technology outcomes. The review combines research from surgical fields, oral health and inflammatory studies to establish if these combined methods create better conditions for implantation and clinical pregnancy success.

The secondary objectives are:

The study examines how chlorhexidine-based perioperative infection control methods affect postoperative complications through their ability to decrease microbial contamination and tissue inflammation and their effect on reducing initial surgical complications that affect ART success rates.

The research investigates how dental health conditions affect blood inflammatory markers, including CRP and IL-6, and determines if dental treatment of oral problems and tongue issues leads to better reproductive results.

The research assesses the scientific basis for using enzymatic therapy with trypsin–chymotrypsin to decrease swelling and promote tissue recovery and shorten postoperative recovery duration, which allows for faster ART procedures.

The research investigates the biological connections between surgical site inflammation and tissue restoration and endometrial readiness for implantation through clinical and physiological data to create a logical explanation.

The research reveals gaps in existing studies while determining vital research paths to develop individualised perioperative protocols for infertility treatment.

The research goals established will determine if a combined perioperative approach produces better fertility results than the current surgical and ART treatment methods.

Methods

The review used a narrative integrative approach to merge existing scientific evidence about infertility treatment perioperative methods through analysis of chlorhexidine antisepsis and oral health status, and trypsin–chymotrypsin enzymatic therapy. The review process located studies which applied the analytical framework to examine perioperative factors that affect surgical recovery and ART outcome success.

The research team performed an extensive literature review through major scientific databases, including PubMed, Scopus and Web of Science. The research analysed studies which investigated perioperative antisepsis and postoperative inflammation and dental and

periodontal health, systemic cytokine responses and enzymatic wound healing processes. The search used different combinations of chlorhexidine and oral health, periodontal inflammation, proteolytic enzymes, postoperative recovery, infertility and ART to retrieve a broad range of relevant studies. The research group has conducted a manual review of the reference lists to identify the necessary studies that may not have been identified by databases during the search.
In the research strategy, the authors incorporated other studies that provided evidence of perioperative inflammatory processes in other clinical approaches in order to obtain methodological precision. The research strategy involved the investigation of the effect that microbial control, periodontal inflammation and postoperative enzymatic changes can have on the systemic cytokine levels due to the lack of adequate data and methodological appropriateness in existing infertility research. The evidence sources applied in the research to examine the biology of implantation are varied, as the success rates of ART are attributed to factors that are outside the knowledge of traditional reproductive medicine. In the review, the researchers analysed research findings in themes rather than systematically using assessment methods.
achieve both detailed conceptual understanding and scientific connections between different fields.

Inclusion and Exclusion Criteria
The review established particular selection criteria to combine data from all three surgical time periods into a single assessment system. The study inclusion criteria consisted of three conditions, which were:
The research studied chlorhexidine-based antiseptic methods for gynecologic, abdominal, and infertility surgical procedures.
The research investigated how dental and mouth infections affect reproductive system cytokines, which control reproductive functions.
The study examined the effects of trypsin–chymotrypsin enzymatic therapy on tissue recovery and inflammation after surgery.

The review analysed clinical study data together with mechanistic research to determine the biological pathways which link these interventions to implantation processes and ART success rates. The review method enabled the combination of different clinical practices through their common inflammatory processes instead of focusing on specific surgical techniques.

The research team established specific boundaries to determine the exact range of their conceptual framework. The research team excluded studies that:
The research studied male infertility cases which needed no surgical treatment or perioperative procedures.
The research examined antiseptic agents together with oral health conditions, which failed to produce any impact on body-wide inflammatory responses.

Used enzymatic formulations which lacked documented proteolytic activity.
The review excluded secondary reviews because they contained theoretical information without experimental data, which was necessary for performing synthesis experiments.
Studies reported reduced postoperative inflammatory markers following chlorhexidine application, which may have implications for subsequent ART cycles.

Rationale for the Narrative Review Approach
The three perioperative domains of antisepsis, oral inflammation and enzymatic therapy stem from different medical specialities, which typical systematic review methods do not combine. The review unites immunological mechanisms with surgical evidence and reproductive-endocrine data through an integrated approach to create a single analytical system. Scientists use research methods to study cause-and-effect relationships while they search for common biological indicators and determine where scientific fields produce conflicting results.

Search Flow and Study Mapping
The analysis required a systematic search approach because different study designs made it impossible to use a standard PRISMA diagram. The research began with database queries about perioperative treatments, which were then organised into three domains based on their cytokine effects. The research design allowed both papers to either give theoretical explanations about the mechanisms or give empirical data about the patient recovery after the surgery.
The review took an integrative approach, but failed to lay down certain criteria for the inclusion or exclusion of studies. The evaluation process evaluated the studies depending on the relationship to the fertility treatment and the timing of surgeries, and their value towards the knowledge of wound healing and inflammatory mechanisms. The review considered any articles that examined microbial control and oral

inflammation, and the pattern of cytokines and tissue healing processes to understand the impact they have on the body's response to the perioperative process in implant and ART cases.
The review did not concentrate on evaluation, but on interpretation, hence it did not include risk-of-bias instruments and formal appraisal checklists. The review evaluated the extent to which the results of the research correlate with biological processes and the evidence that demonstrates better reproductive results due to better perioperative care.
The researchers used thematic analysis to analyse collections of studies collected. The research studies were divided into three domains, which focused on the three perioperative areas of interest, including antiseptic measures and oral-health–related inflammatory pathways and enzymatic modulation of postoperative tissue responses.

Results

Overview of Included Studies

The final search produced multiple studies which investigated the three perioperative areas affecting infertility treatment: chlorhexidine antisepsis and oral health status, and enzymatic therapy with trypsin–chymotrypsin. The research included randomised controlled trials, prospective cohort studies and case–control analyses, and mechanistic clinical investigations which examined systemic inflammation. The research employed distinct design methods with different study participants to prove that effective perioperative inflammation management produces superior postoperative outcomes and enhanced ART success rates in particular situations.

Findings Related to Chlorhexidine Antisepsis

The research results showed that chlorhexidine proved effective in lowering postoperative bacterial contamination, and it decreased the risk of developing surgical complications during the early recovery period.
The studies which used chlorhexidine for gynecologic and abdominal procedures showed decreased wound infections and reduced erythema and late-onset inflammation. Multiple studies showed that lower postoperative infection rates and inflammation levels correlated with decreased serum CRP and IL-6 levels, which are known to affect endometrial receptivity. The study shows that chlorhexidine application during infertility procedures leads to long-term inflammation, which produces better results for future ART implantation procedures.
The immunological effects of Chlorhexidine exceed its ability to reduce postoperative infection rates. The treatment of patients with chlorhexidine before gynecologic and abdominal surgeries resulted in faster IL-6 and CRP decreases than povidone–iodine treatment. The start of ART depends on inflammatory marker normalisation because brief IL-6 increases can damage uterine blood vessels and interfere with progesterone-induced endometrial receptivity. The findings suggest that chlorhexidine may contribute to improved reproductive outcomes by stabilising cytokine activity during the implantation period.

Findings Related to Oral Health and Systemic Inflammation

Research studies demonstrate that oral pathology leads to body-wide inflammation spread according to studies. The body maintains a persistent inflammatory condition through periodontal disease and unhealed extraction sites and tongue lesions, which result in elevated CRP and IL-6 levels. Studies have reported associations between improved oral health status and favourable systemic inflammatory profiles, which may influence reproductive outcomes. The body maintains active inflammatory sites, which produce cytokines that interfere with early pregnancy development through their disruption of implantation and placental formation. The research evidence indicates that patients beginning infertility treatment need to undergo complete oral health evaluations followed by vital dental procedures before starting their treatment.
The research shows that oral inflammation causes reproductive changes by activating distant body systems instead of requiring periodontal tissue inflammation to happen. Research findings show that untreated dental conditions lead to ongoing, minimal cytokine leakage, including IL-6, TNF-α, and CRP, which spread throughout the body to interfere with endometrial development during implantation. The research results demonstrated that women who received periodontal therapy before starting ART treatment achieved better endometrial blood flow and improved alignment of the luteal phase endometrium than women who did not receive treatment. The research shows that the oral cavity functions as a persistent inflammatory site, which affects blood flow in the uterus and progesterone-induced decidualization to impact implantation success even when embryos have excellent quality. The immunologic environment, which determines ART success, requires oral health treatment as an essential medical practice.

Findings Related to Trypsin–Chymotrypsin Enzymatic Therapy

Studies about proteolytic enzymatic therapy show that patients who get trypsin–chymotrypsin therapy experience better postoperative results because their swelling and bruising symptoms reduce and their soft tissues become more flexible. The enzyme combination outperformed conventional postoperative care because it accelerated oedema reduction and tissue structure improvement, which suggests its ability to affect the first stage of surgical inflammation. Research studies have proven that patients experience better comfort while requiring reduced pain medication and their bodies recover at an accelerated rate. The available research indicates that enzymatic therapy could benefit ART cycle timing because it accelerates wound healing and reduces postoperative inflammation.

The research findings demonstrated that enzymatic treatment modified surgical tissue responses, which affect the readiness of ART. Research studies that combined trypsin and chymotrypsin enzymes for enzyme therapy achieved faster tissue oedema resolution, reduced inflammatory exudate accumulation, and enhanced microvascular function at surgical sites. The observed changes hold clinical value because postoperative swelling and extended inflammation trigger increased cytokine production, which extends the time needed for optimal implantation readiness. The research findings demonstrate no direct relationship between enzymatic therapy and reproductive success, yet the therapeutic advantages for inflammation and uterine receptivity suggest that enzymatic treatment could help patients who need to start ART right away. The available evidence confirms proteolytic therapy as a biologically valid supportive treatment for patients who need urgent ART procedures, but researchers need to study its full reproductive effects.

Systemic Inflammation as a Converging Mechanism

The different research approaches revealed that systemic inflammation serves as the shared biological factor which connects all three treatment methods.

The microbial activation of inflammation decreases when patients receive chlorhexidine treatment.

The process of oral health optimisation helps patients remove ongoing inflammatory triggers which affect their bodies.

The enzymatic treatment method enables patients to recover from postoperative inflammation at an accelerated pace.

Studies indicate that reproductive success is enhanced when CRP and IL-6 levels decrease because this leads to thicker endometrial tissue and enhanced uterine blood flow, which occasionally results in better implantation success. The research evidence supports the theory that reducing body-wide inflammation may be associated with assisted reproductive technology.

The three interventions share a common immunological pathway, which depends on IL-6 and CRP and endothelial signalling pathways that develop from these factors. Studies show that lower IL-6 levels lead to better uterine blood flow and thicker endometrial tissue, which enhances the chances of successful implantation. The anti-inflammatory effects of each treatment approach work through different initial mechanisms, which include chlorhexidine's microbial load reduction and oral-health optimisation's cytokine control and enzymatic therapy's fast postoperative oedema resolution. The separate treatment pathways demonstrate that ART success depends on minimal changes in the inflammatory state surrounding implantation.

ART Outcomes: Emerging but Incomplete Evidence

The research included studies which measured ART parameters, including implantation and clinical pregnancy, and live birth rates, but only a few studies directly evaluated these parameters. The research data produced identical results between the different study groups.

The research showed that patients who received optimised oral care achieved better pregnancy outcomes.

The success rate of implantation improved when patients demonstrated lower postoperative inflammation levels.

Enzymatic therapy led to quicker patient recovery, which enabled them to attempt ART procedures at an earlier time or with better results.

The current evidence fails to establish definitive cause-and-effect relationships because studies used different sizes and follow-up durations and measured outcomes through various methods. Future research needs to conduct well-planned prospective studies which use uniform perioperative protocols to measure how these three interventions work together. The available studies show consistent patterns which link these treatment approaches to better ART results, although direct evidence between these strategies and ART outcomes is scarce. The oral health optimisation, plus the use of chlorhexidine-based antisepsis therapy, results in the improvement of

the outcome of implantation and clinical pregnancy, primarily in patients who demonstrate a reduction in the levels of the inflammatory markers after the given treatment. Patients who were subjected to proteolytic enzyme treatment in order to recover faster had better endometrial health when commencing their ART cycles. The current relationship between improved perioperative inflammatory care and improved reproductive outcomes indicates that the two aspects may be biologically related. This paper reveals that minor biological alterations that occur during operating times and are usually overlooked by fertility physicians influence the rate of ART success.
Table 1 summarises the evidence across the three domains.

Table 1: Summary of Evidence Across the Three Intervention Domains

Intervention	Evidence on Postoperative Outcomes	Evidence on Inflammation (CRP/IL-6)	Evidence on ART Outcomes	Overall Interpretation
Chlorhexidine Antisepsis	↓ Infection, ↓ wound complications	↓ CRP and ↓ IL-6 in several studies	Suggestive but indirect	Likely beneficial for perioperative optimisation
Oral Health Optimisation	Not directly surgical	Strong reduction in systemic cytokines	↑ Pregnancy rates in multiple studies	Significant impact on systemic reproductive environment
Trypsin–Chymotrypsin Therapy	↓ Oedema, ↑ healing speed	Moderate evidence for ↓ IL-6	Limited but promising	Likely improves readiness for ART cycles

Overall Interpretation of the Evidence
It has been demonstrated that there is a biologically upheld model of perioperative antisepsis and oral health stabilisation and enzymatic support that work on different pathways to reduce inflammation.

Discussion
The results of this narrative review suggest that perioperative inflammation can be a significant issue that affects the reproductive outcomes of patients undergoing infertility-related surgery before assisted reproductive technology (ART). Even though the three interventions reviewed in this paper have their source in various clinical areas, the current evidence appears to indicate that they can overlap on the same biological pathways that have an effect on postoperative recovery and implantation potential.
These perioperative approaches seem to play off with a common inflammatory network that can play a role in determining the success of implantation. Although these spheres of care might seem unrelated at first, they all lead to the regulation of systemic activity of cytokines, microbial load, and tissue recovery throughout ART treatment cycles. The slight differences in inflammatory factors like IL-6 and CRP at the times of perioperative procedures can affect the process of endometrial receptivity and implantation, which are extremely sensitive to the immune control (10).
The use of chlorhexidine in the perioperative preparation may help to prevent surgical site and postoperative inflammatory complications, according to the evidence. Research conducted on the measurement of surgical antisepsis has indicated that protocols using chlorhexidine have been found to achieve a better reduction of microbial load and better control of inflammatory responses in the early postoperative period in comparison to other antiseptic agents (11). A decrease in postoperative infection and inflammation can help to achieve better tissue healing and a more positive biological condition of implantation.

Oral Health as a Driver of Systemic Inflammation and Reproductive Outcomes
The differences in results between studies cannot always be negated by the proposed hypothesis because the majority of the existing studies have studied perioperative inflammation through solitary clinical lenses. There are a lot of past studies that have involved individual disciplines, e.g. gynaecologic surgery, dentistry or postoperative care, without conducting any studies to see their overall effect on reproductive physiology. By synthesising these independent lines of evidence, the current review hypothesises that perioperative management of infertility can be more of a systemic approach to stabilise inflammatory reactions before embryo transfer.

Enzymatic Therapy and Accelerated Tissue Healing
Enzymatic therapy with trypsin-chymotrypsin has already been mentioned to decrease postoperative

swelling, tissue pressure, and tissue inflammatory exudate and increase rapid structural tissue recovery. Other experimental results show that chymotrypsin can control inflammatory mediators and oxidative stress responses in biological tissues, which confirms the possibility of this protein in regulating postoperative inflammatory responses (12).

Clinical and experimental evidence indicates that these enzymes can help in degrading inflammatory mediators and necrotic tissue substances, which increases the rate of healing of surgical inflammation (13).

Even though there is still no direct evidence as to the fact that enzymatic therapy can lead to better results of ART, the possible speed of postoperative recovery can be achieved with the help of enzymatic therapies, which may provide the possibility to initiate ART cycles under better physiological parameters.

Integrative Interpretation and Mechanistic Convergence

The current review offers the idea that chlorhexidine antisepsis, oral health optimisation, and enzymatic therapy could have various initial processes, but eventually, they affect systemic inflammatory control.

The main mechanism of action of chlorhexidine is the suppression of inflammatory activation by microorganisms. Oral health optimisation removes chronic cavity inflammatory reservoirs in the oral cavity. Enzymatic therapy speeds up the process of postoperative inflammatory processes. These mechanisms together can be used to stabilise. systemic inflammatory signalling during the critical peri-implantation period.

Successful implantation requires a delicate immunological balance involving both pro- and anti-inflammatory cytokines, including IL-6, IL-1β, TNF-α, and IL-10, which regulate endometrial receptivity, vascular remodelling, and trophoblast invasion (14). Disruption of this balance by infection, persistent inflammation, or prolonged postoperative tissue injury may negatively affect implantation timing and embryo-endometrial synchrony.

Future studies need to create uniform surgical methods which will enable researchers to analyse these interventions through a complete system assessment because current evidence exists in isolated fragments. The effectiveness of chlorhexidine antisepsis with periodontal therapy and proteolytic enzymes for systemic cytokine regulation and endometrial receptivity needs to be proven through future prospective clinical trials. The research requires established inflammatory markers for its analysis, and it needs to identify common inflammatory indicators between oral and systemic inflammation and monitor endometrial blood flow and uterine lining development at specific time points. The research of perioperative inflammation timing requires interdisciplinary collaboration between reproductive medicine, oral biology and surgical immunology to establish when inflammation reaches its highest point, which affects ART success rates. Research needs to fill existing knowledge gaps to discover the best peri-implantation environment for infertile patients.

Comparison With Previous Reviews and Remaining Gaps

Bharath et al. (2025) studied chlorhexidine applications for surgical infection control in their previous work. The study by Altieri et al. (The 2021 research study investigated how periodontal health status affects fertility. The research by Grande et al. (2022) studied enzymatic therapy for postoperative recovery, but no study has combined this approach with reproductive assessment. The current review combines various research fields to prove that a reproductive-centred perioperative model demonstrates potential as an effective treatment method.

The research study identifies multiple critical knowledge gaps which existing studies have not addressed.

The current research lacks randomised trials which evaluate the complete set of interventions for ART patients.

The research uses different methods to measure implantation success, inflammation markers, and wound healing outcomes. The absence of standardised perioperative protocols makes cross-study comparison difficult.

Addressing these gaps will require coordinated efforts between reproductive endocrinologists, oral health specialists, and surgical teams.

The three perioperative domains produce evidence which supports a single conceptual framework that shows microbial control and periodontal stability and postoperative enzymatic modulation work together as separate controls within the immune system that controls implantation. The three interventions use different initial pathways to reach their common effect on cytokine regulation, endothelial activation and progesterone-induced endometrial transformation. The integrated method shows that infertility treatment needs a single approach to preserve inflammatory stability during the essential time when implantation ability forms. The review shows that reproductive success

depends on controlled systemic inflammation while demonstrating that ART success needs equal focus on perioperative physiological management and embryologic and hormonal optimisation.

Study Limitations
The review contains limitations because research findings differ between studies, and there is insufficient infertility-focused research with standardised measurement criteria for postoperative inflammation and oral health status. The research depends on indirect evidence because there are no studies that test all three interventions together in one study design. The absence of randomised controlled trials that study combined perioperative strategies makes it essential to conduct more advanced research to verify their effects on reproduction. The review combines existing research findings through a narrative approach instead of using a structured narrative review method.

Conclusion
The evidence from this review shows that perioperative inflammation causes reproductive problems and affects ART success because it controls inflammatory reactions. The common biological process between these interventions explains why patients who receive these treatments experience better healing outcomes, decreased cytokine levels, and improved pregnancy success rates in specific studies. The three interventions from different medical fields work through identical biological processes to decrease body-wide and local swelling while creating faster recovery with better stability after surgery. The research demonstrates that a unified perioperative system, which connects medical specialities, creates the best conditions for implantation and successful early pregnancy results.

List of Abbreviations
ART: Assisted Reproductive Technology
CRP: C-Reactive Protein
IL-6: Interleukin-6
TNF-α: Tumour Necrosis Factor Alpha
IVF: In Vitro Fertilisation
CHX: Chlorhexidine

Declarations
Ethics approval and consent to participate
Ethical approval was not required for this study because it is a narrative review based exclusively on previously published data. No human participants, animals, or identifiable personal data were involved in this research.

Consent for Publication
All authors gave consent for publication of the work under the Creative Commons Attribution-Non-Commercial 4.0 license.

Availability of data and materials
All data analysed during this study are derived from previously published articles and publicly available sources.

Competing interests
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Authors' contributions
Study idea and supervision: MTO; Literature research and data collection: MHR; Data analysis and interpretation: MSA; Drafting and manuscript revision: AAS; Critical manuscript revision and final editing: NKZ; All authors read and approved the final version of the manuscript.

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