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Original Article

Evaluation of Angiogenic Potential of Baghdadite, Mineral Trioxide Agregate, and their Combination Using the Yolk Sac Membrane Model

Ankita Tapkir[1], *Nilesh Rathi*[1], *Ankita Mathur*[2], *Avinash Sanap*[3], *Surabhi Sinnarkar*[1], *Nishant Mante*[3]

[1]*Department of Pedodontics and Preventive Dentistry, Dr. D. Y. Patil Dental College and Hospital, Dr. D. Y. Patil Vidyapeeth, Pimpri, Pune, India*
[2]*Department of Dental Research Cell, Dr. D. Y. Patil Dental College and Hospital, Dr. D. Y. Patil Vidyapeeth, Pune, India*
[3]*Regenerative Medicine Laboratory, Dr. D. Y. Patil Dental College and Hospital, Dr. D. Y. Patil Vidyapeeth, Pimpri, Pune, India*

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Corresponding Author:
Ankita Mathur, Department of Dental Cell Research, Dr. DY Patil Dental College and Hospital, Dr. DY Patil Vidyapeeth, Pune 411018, Maharashtra, India
E-mail: ankita.statsense@gmail.com

Abstract

Background: Biomaterials that promote neovascularization are of great value in regenerative endodontics. Mineral Trioxide Aggregate (MTA) is commonly employed for pulp capping, whereas Baghdadite, a bioactive calcium-zirconium-silicate ceramic, has been reported to be useful in inducing angiogenesis. Comparing the efficacy of Baghdadite, MTA, and their combination, however, is not well investigated. This study aims to assess and compare the angiogenic potential of Baghdadite, MTA, and their combination at two concentrations with the chick embryo yolk sac membrane (YSM) model.

Methods: 70 fertilized White Leghorn eggs were incubated to promote the yolk sac vasculature. Seven experimental groups were MTA (5 µg and 10 µg), Baghdadite (5 µg and 10 µg), MTA+Baghdadite (5 µg and 10 µg), and a control group. The experimental groups were exposed on the yolk sac membrane and incubated for 48 hours. Angiogenesis was quantitatively evaluated by Wimasis image analysis software for vessel density, total length of vessel network, and branching points.

Results: The interaction between MTA and Baghdadite at 5 µg revealed the maximum angiogenic potential with a vessel density of 17.6%, vascular length of 13,515.9 pixels, and 213 branching points. Baghdadite without the addition of MTA performed better than MTA at both the concentrations. MTA at 10 µg revealed relatively lower angiogenic ability, indicating dose-dependent cytotoxicity.

Conclusion: Baghdadite markedly promotes angiogenesis, and when used in combination with MTA at lower levels, exhibits a synergistic effect. These results validate its potential for use in regenerative endodontic procedures involving neovascularization, particularly in vital pulp therapy.

Keywords: angiogenesis, Baghdadite, Mineral Trioxide Aggregate (MTA), regenerative endodontics, yolk sac membrane model

Introduction

Angiogenesis, the development of new blood vessels from established vasculature, is fundamental to dental pulp tissue regeneration and repair responses to injury or treatment.[1,2] Successful vascularization is important to preserve pulp tissue viability, provide necessary nutrients, and enable removal of metabolic waste, having a major bearing on the success of regenerative endodontic therapy.[3,4] A number of biomaterials have been investigated to induce angiogenesis because of their possibility of promoting pulp regeneration and repair, leading to better clinical outcomes in endodontic therapies.[5,6]

Mineral Trioxide Aggregate (MTA) has gained popularity as an extensively utilized biomaterial in endodontics for pulp capping, apexogenesis, and the creation of an apical barrier because of its high biocompatibility, seal, and regeneration properties.[7,8] MTA enables regeneration by releasing calcium ions, which enhance cell proliferation, differentiation, and angiogenic pathways, especially through upregulation of vascular endothelial growth factor (VEGF).[9] Dayta in the study suggests that biological activity of MTA, such as its angiogenic potential, varies very much with concentration, and increased doses may lower cell viability based on the alkaline pH and excess release of calcium.[10,11]

Recently, Baghdadite, calcium zirconium silicate bioceramic, has been found to be a potential material in biomedical fields due to its better bioactivity, degraded controlled rate, and intrinsic ability to promote osteogenesis and angiogenesis.[12] Baghdadite's angiogenic capability has been linked to the release of bioactive ions, especially calcium and silicate ions, that may influence key cell signal pathways, leading to improved endothelial cell migration and proliferation as fundamental elements of vascular development.[13] Evidence from experiments indicates Baghdadite's high ability to produce vascularized tissue formation through VEGF-mediated pathways, and this makes it an efficient tool for tissue engineering.[12,14]

While the angiogenic capacity of individual MTA and baghdadite is becoming well understood, their combined application has yet to be widely explored. The potential synergistic effect of combining baghdadite's strong angiogenic capacity with MTA's regenerative effects may enhance clinical performance, perhaps overcoming inefficiencies relative to greater concentrations of MTA alone. Therefore, the current study intends to comparatively analyze the potential of Baghdadite, MTA, and their combination regarding angiogenesis through the chick embryo yolk sac membrane (YSM) model.

Materials and Methods

Study design and setting

This *in vivo* experimental study was conducted to analyze the angiogenic potential of Baghdadite, MTA, and their combination in the chick embryo YSM model. The experiment was performed under sterile conditions in the Regenerative Medicine Laboratory, Dr. D. Y. Patil Dental College and Hospital, Pune, India.

Experimental materials and group allocation

The materials used in this research were MTA (Angelus Indústria del, Londrina, Brazil) and Baghdadite powder / Baghdadite nanopowder (Nano Research Elements (Nanorh), Dhanora Jattan (Kurukshetra), India). For dose-dependent effects, individual samples of both materials were tested at 5 µg and 10 µg concentrations. Combinations of MTA and Baghdadite were also prepared in 1:1 weight ratios at both 5 µg and 10 µg total concentrations. The materials were dissolved in distilled water. There were seven groups in the study: MTA 5 µg, MTA 10 µg, Baghdadite 5 µg, Baghdadite 10 µg, MTA + Baghdadite 5 µg, MTA + Baghdadite 10 µg, and a control group receiving no material application.

The concentrations of 5 µg and 10 µg for both MTA and Baghdadite were chosen to reflect a low and high dose range capable of producing observable angiogenic responses without overwhelming the YSM model. These levels allowed for the assessment of dose-dependent effects. For combination groups, MTA and baghdadite were mixed in a 1:1 weight ratio to maintain consistency in total applied dose and enable evaluation of potential synergistic interactions under equal contribution of both materials.

Each group, including the control and the six experimental conditions, consisted of 10 fertilized eggs, bringing the total sample size to 70.

All test materials were suspended in sterile distilled water and handled under aseptic conditions within a laminar airflow cabinet. As the suspensions contained particulate matter (non-soluble fractions of MTA and

Baghdadite), filtration (e.g., 0.22 µm) was not employed to preserve the integrity and dosage of the particulate material. The preparations were immediately used following mixing to ensure sterility and consistency.

YSM assay procedure

White Leghorn chicken eggs fertilized (n=70) were obtained (Venkateshwara hatcheries Pvt Ltd, Maharashtra, India) and incubated at 37.5°C with 70-80% relative humidity for 72 hours to enable development of the vascular network in the yolk sac. Following incubation, about 5 mL of albumin was removed from each egg by using a sterile syringe to reduce the developing embryo and enable visualization of the membrane in the yolk sac. A 3 cm×3 cm window was then precisely cut on the eggshell covering the air sac under aseptic conditions with a sterile rotary blade without any damage to the underlying vasculature.

After establishing the window, the test material were carefully exposed on the YSM. For the control group, the membrane was not exposed to any material. The eggs were sealed using sterile parafilm and incubated for another 24 hours. Figure 1 illustrates the procedural workflow of the YSM angiogenesis model.

Imaging and quantitative assessment of angiogenesis

At 24 hours of exposure, the YSM were examined using a Leica EZ4 HD stereo microscope (Leica Microsystems; 8-35× magnification, integrated 3 MP camera, LED illumination). The images were analyzed using Wimasis Image Analysis software (Wimasis, trial version, 2025 release; Wimasis GmbH, Munich, Germany), which gave objective quantification of angiogenic parameters. Representative images of angiogenic response for Baghdadite, MTA, and their combination, both before and after treatment, as well as the Wimasis-based analysis output, are shown in Figure 2.

Three specific parameters were quantified to determine angiogenesis: vessel density (in terms of percentage vascular area within the specified field), total length of the vessel network (in pixels), and number of vascular branching points (a measure of network complexity). Results for each sample were ascertained as a mean of three independent fields. The value for each parameter was determined separately for all test groups and compared with the control.

For each sample, three non-overlapping fields of interest were selected from the peripheral vascular zone of YSM, an area that consistently exhibited dense and organized capillary patterns. Field selection was semi-randomized within this predefined anatomical region to ensure consistency across all samples and minimize observer bias. All images were captured at a fixed magnification (×20) using the Leica EZ4 HD stereomicroscope, with a standardized field size of 1920×1080 pixels. These images were analyzed using Wimasis image analysis software, with identical thresholding and measurement parameters applied to all fields.

The image analysis was performed in a blinded manner, with the evaluator unaware of the treatment group assignments during quantification of angiogenic parameters.

Ethical considerations

The study conformed to institutional animal studies ethical standards. Embryonated eggs were utilized at a pre-hatch point (prior to day 7 of development), in keeping with global guidelines for non-animal status during

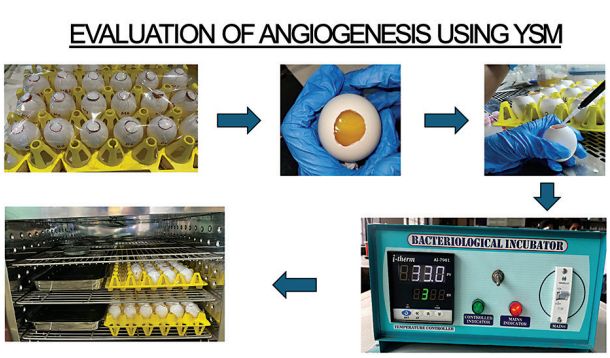

Figure 1: Procedural steps for determining the angiogenic potential using yolk sac model.

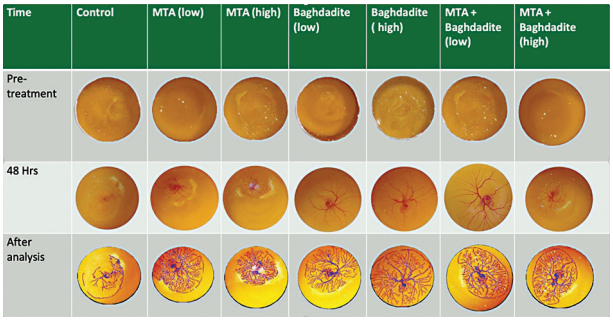

Figure 2: Images of Baghdadite, Mineral Trioxide Aggregate and its combination at different concentrations pretreatment, post treatment and after analysis using wimasis software.

this embryonic phase. All procedures conformed to the institutional research and biosafety ethics policies.

Results

Table 1 and Figure 3 demonstrates vessel density percentages in all study groups. The control group that had no biomaterial application had the lowest vessel density, i.e., 6.8%, representing baseline angiogenesis in the YSM. 5 µg application of MTA increased the vessel density significantly to 12.7%, whereas 10 µg of MTA caused a somewhat lower density of 10.9%, i.e., a possible dose-dependent inhibitory effect at higher doses. Baghdadite alone exhibited better angiogenic stimulation with 17.1% at 5 µg and 17.8% at 10 µg, which shows that both concentrations significantly enhanced blood vessel formation. Importantly, the mixture of MTA and baghdadite at 5 µg resulted in a vessel density of 17.6%, quite similar to that of Baghdadite alone at 10 µg, and inferred a synergistic effect. But the combination at 10 µg yielded a slightly decreased vessel density of 15.1%, showing that although synergistic effects are present at smaller concentrations, increased doses can cause a decline in angiogenic response.

The findings illustrated in Table 2 further support the vessel density results by measuring the overall vessel network length in pixels. Figure 4 shows the total vessels network length of all the experimental groups. In the control group, an average minimum vascular network length of 2757.4 pixels was observed, ensuring minimal baseline angiogenic activity. Conversely, MTA at 5 µg significantly lengthened network length to 10,909.1 pixels and MTA at 10 µg shortened it to 5099.9 pixels, again suggesting a probable cytotoxic or inhibitory effect at increased concentrations. Baghdadite at 5 µg yielded a network length of 12,900.1 pixels, further validating its robust angiogenic profile. Whereas Baghdadite at 10 µg exhibited the slight decrease to 10,460.1 pixels, it nevertheless far surpassed MTA alone. Significantly, the combination group at 5 µg exhibited the best overall vessel length of 13,515.9 pixels, as a measure of synergistic improvement of the angiogenic network formation. Yet, the combination at 10 µg came in with only 6289.3 pixels, showing a drastic fall and further emphasizing the finding that greater concentrations potentially inhibit angiogenic potential.

Table 1: Vessel density (%).

Group	Vessel Density (%)
Control	6.8
MTA 5 µg	12.7
MTA 10 µg	10.9
Baghdadite 5 µg	17.1
Baghdadite 10 µg	17.8
MTA + Baghdadite 5 µg	17.6
MTA + Baghdadite 10 µg	15.1

Table 2: Total vessel network length (pixels).

Group	Vessel Network Length (px)
Control	2757.4
MTA 5 µg	10909.1
MTA 10 µg	5099.9
Baghdadite 5 µg	12900.1
Baghdadite 10 µg	10460.1
MTA + baghdadite 5 µg	13515.9
MTA + baghdadite 10 µg	6289.3

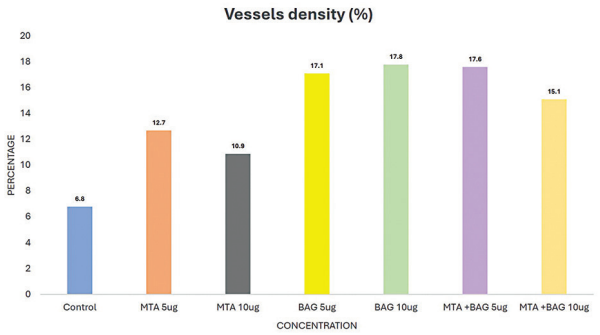

Figure 3: Vessels density of Baghdadite, Mineral Trioxide Aggregate and its combination at different concentrations.

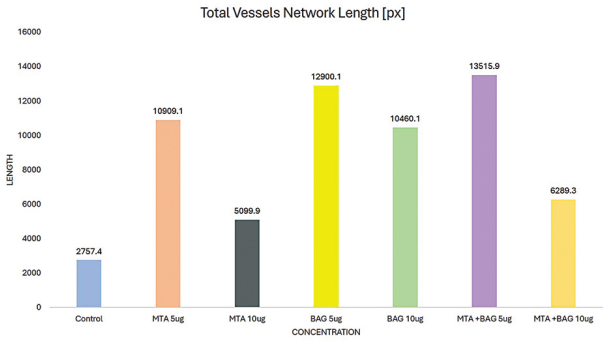

Figure 4: Total vessels network length of Baghdadite, Mineral Trioxide Aggregate and its combination at different concentrations.

Table 3 and Figure 5 summarizes the number of branching points in the vascular network as a parameter of network complexity and functional angiogenesis. The control group had 65 branching points, reflecting minimal vascular branching. MTA application at 5 µg and 10 µg resulted in comparable outcomes, with 151 and 153 branching points, respectively. Although both concentrations were better than the control, the reaction was moderate. Baghdadite at 5 µg produced 206 branching points, and 10 µg produced 179, both of which indicate a remarkable increase in vascular complexity. The MTA + Baghdadite combination at 5 µg performed the best in the number of branching points at 213, with its efficiency in promoting new vessel growth and increasing network connectivity. In contrast, the 10 µg combination group decreased to 170 branching points, again indicating that high concentrations can undermine pro-angiogenic activity, perhaps through high levels of ion release or shifting microenvironmental pH.

Discussion

The present study scientifically assessed and compared the angiogenic value of Baghdadite, MTA, and their mixture using the chick embryo YSM model. The results clearly indicate that Baghdadite alone and in combination with MTA significantly increased angiogenesis relative to MTA alone. Most significantly, the blend of Baghdadite and MTA at 5 µg concentration demonstrated a synergistic pro-angiogenic effect, as reflected in the highest vessel density (17.6%), longest vessel length (13,515.9 pixels), and highest number of branching points (213). Conversely, greater concentrations, especially MTA at 10 µg, had diminished angiogenic activity, arguably due to likely cytotoxicity by alkaline pH or over-release of calcium ions.

Table 3: Total branching points.

Group	Branching Points
Control	65
MTA 5 µg	151
MTA 10 µg	153
Baghdadite 5 µg	206
Baghdadite 10 µg	179
MTA + baghdadite 5 µg	213
MTA + baghdadite 10 µg	170

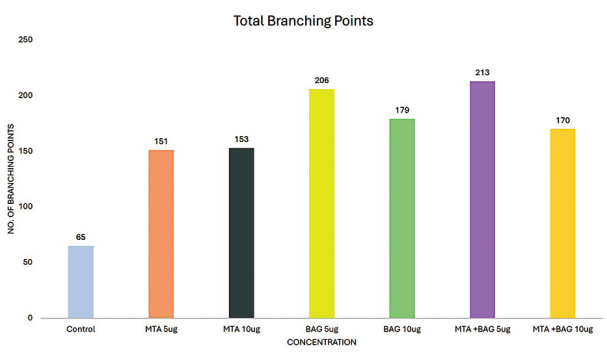

Figure 5: Total branching points of Baghdadite, Mineral Trioxide Aggregate and its combination at different concentrations.

The findings of this study highlight baghdadite's pronounced pro-angiogenic potential, consistent with its established bioactivity as a calcium–zirconium–silicate ceramic The resultant vessel density, network length, and branching points with Baghdadite alone (5 µg and 10 µg) confirm the hypothesis that its ionic dissolution products, predominantly calcium and silicate ions, are largely responsible for promoting angiogenesis. These ions have also been known to evoke endothelial cell signaling pathways, including those involving VEGF, that stimulate migration, proliferation, and vascular sprouting. Furthermore, the gradual and long-term release of ions by Baghdadite is capable of establishing a more favorable microenvironment for endothelial activity compared to that of MTA, which exhibits cytotoxicity at higher concentrations due to excessive release of ions and high pH.[12,13] The consistency of angiogenic response at both concentrations of Baghdadite validates its application in regenerative endodontic treatment where vascular support is crucial for repair and regeneration of the tissue.

The results of this study agree with the general trend in regenerative dentistry, in which improved vascularization is essential for the successful repair of pulp-dentin complexes following therapeutic treatments.[15,16] Proper vascularization ensures optimal delivery of nutrients and oxygen, thus stimulating cellular growth, differentiation, and tissue development.[17,18] The ability of Baghdadite to cause a vigorous angiogenic response seen in our research is especially encouraging because proper vascularization is an important step in pulp tissue regeneration and for successful clinical results in endodontics.

Baghdadite, a calcium zirconium silicate bioceramic, has gained significant interest based on its biocompatibility, sustained degradation, and bioactivity.[5] The angiogenic activity of Baghdadite is mainly due to its

dissolution products in ionic form, specifically calcium, zirconium, and silicate ions, known to promote angiogenesis by stimulating endothelial cell growth, migration, and differentiation.[6,19] Sadeghzade *et al.,* elaborately reviewed the biomedical potential of Baghdadite with a focus on its osteoinductive and pro-angiogenic biomaterial potential due mainly to controlled ionic release, especially calcium, zirconium, and silicate ions, regulating cellular responses critical for tissue regeneration.[12] The ions were shown to enhance cellular migration, proliferation, and differentiation, most notably in endothelial cells, playing a critical role in increased angiogenesis.[5,20] In addition, the ion-induced angiogenesis that occurred with Baghdadite in the present work also increases its likelihood of involvement in dental pulp regeneration, considering the life-sustaining role of vascularization in pulp vitality and function.[6]

On the other hand, whereas MTA is well-rooted as an endodontic biomaterial with strong evidence supporting its clinical effectiveness in vital pulp treatments like apexogenesis and direct pulp capping, its angiogenic activity, though desirable, seems extremely concentration-dependent.[21,22] Our findings indicated decreased angiogenic activity with higher doses (10 µg), which is consistent with the results from earlier studies showing that an increased release of calcium ions and consequent increase in pH can cause cytotoxicity on cells and inhibit the formation of blood vessels.[4,23] Parirokh and Torabinejad comprehensively discussed biocompatibility of MTA, stating that though it has desirable regenerative properties, high doses and extended exposure could diminish cell viability and affect therapeutic outcomes, highlighting the importance of optimal dosing in its clinical application.[10]

The synergistic action of the Baghdadite-MTA mixture at lower concentrations (5 µg) in this study presents a great clinical relevance. Combining Baghdadite's pro-angiogenic properties with MTA's sealing and regenerative capabilities could potentially optimize pulp regeneration outcomes. This synergism might be attributable to the complementary ionic profile released from the mixture, balancing angiogenic signaling without inducing excessive alkalinity or cytotoxicity. This result corresponds with emerging trends in regenerative endodontics, advocating the combination of different biomaterials to achieve comprehensive tissue regeneration.[12,24,25]

Notably, the idea of using blends of biomaterials to promote their biological activity has been advocated for by past research using different biomaterials in regenerative dentistry. As an example, Salehi *et al*., illustrated that the combination of bioactive ceramics and polymers enhanced angiogenesis and osteogenesis compared to single material in bone regeneration models.[14] The authors used a composite scaffold made of polylactic acid-Baghdadite and chitosan loaded with VEGF and achieved much enhanced angiogenesis and bone regeneration relative to monolithic scaffolds, thereby stressing the advantage of biomaterial composites in accelerating tissue healing through combined biological processes.[14] Our study carries this principle forward to regenerative endodontics specifically, demarcating the significance of well-optimized combinations leading to the desired therapeutic effects.

The chick embryo chorioallantoic membrane (CAM) model is an established and widely used *in vivo* model system for the study of angiogenesis. It has the benefits of being ethically acceptable, cost-effective, and permitting direct observation and measurement of angiogenic activity. The CAM model has been used in many studies to evaluate the angiogenic capacity of biomaterials and drugs.[26-28] In line with earlier reports, our approach allowed for objective, accurate quantification of angiogenic parameters with Wimasis software, and thus ensured reproducibility and less observer bias.[29]

From a clinical perspective, Baghdadite's physical properties, including porosity, structural integrity, and degradation profile, hold significant relevance in determining its suitability for regenerative endodontic procedures and vital pulp therapy. Baghdadite has a moderately porous structure, which is conducive to ionic exchange and angiogenesis while still being mechanically stable enough for intracanal use.[12,19] In contrast to certain traditional bioceramics that sacrifice strength in favor of greater porosity, Baghdadite has an ideal balance between compressive strength and bioactivity, and it is structurally sound even at physiological conditions.[12,20] This is a significant aspect especially in applications like VPT, wherein the material is exposed to occlusal forces and fluids. Moreover, although MTA is well established due to its excellent sealing property for endodontic applications[10], the addition of Baghdadite may improve the biological profile without compromising the seal especially at optimized low concentrations. Despite the fact

that there is limited data regarding Baghdadite's sealing potential in clinical situations, its inclusion into hybrid bioceramic formulations is promising for imminent use. Furthermore, having a minimum depth of placement is necessary to ensure proper sealing and regenerative response, such factors should be studied further in preclinical models so as to determine clinical guidelines.[21,22]

It should be noted that the used concentrations in this research (5 µg and 10 µg) were chosen to allow sensitive detection of angiogenic activity in the YSM model but prevent vascular occlusion or structural damage. Although these values are lower than those found in clinical MTA use, the purpose of the current investigation was not to mimic clinical dosing but to screen comparative pro-angiogenic activity of the materials alone and in combination. Preparation of set cement forms or extracts according to ISO 10993-12 would be critical in later cytocompatibility investigations assessing clinical-grade formulations. Further research using MTA–Baghdadite composite cements at clinically appropriate doses is justified to verify these results under translationally relevant conditions.

Future studies would also aim to further identify the molecular and cellular processes involved in Baghdadite-induced angiogenesis. In-depth analysis of particular signaling pathways invoked by Baghdadite, e.g., VEGF receptor pathways, hypoxia-inducible factor (HIF-1α), and subsequent angiogenic cascades, would be essential to provide key information in maximizing clinical applications.[30,31] Moreover, additional confirmation of the resultant synergistic effects in more clinically applicable models, for instance, rodent pulpal regeneration models or human-derived dental pulp stem cell (DPSC) cultures, would add to the translational value of our results.

Although the YSM assay used in this study provides a speedy and affordable platform to assess early angiogenic reactions, it mainly records short-term neovascularization patterns within a 24-hour time frame. While increasing the observation time to 48 hours might permit additional measurement of vessel remodeling and maturation, preserving the yolk sac and keeping embryo disturbance low beyond 24 hours proves to be practically difficult. Notably, YSM model differs from the better-studied CAM assay, which is based on a different extra-embryonic membrane architecture and developmental schedule. The differences have been resolved to prevent conceptual duplication.

It should further be noted that the YSM model, although appropriate for high-throughput screening of angiogenic capacity, does not mimic the intricate cellular and matrix structure of the dental pulp. Thus, the present findings, although promising, need to be ascertained in clinically relevant *in vivo* models, e.g., regenerative endodontic treatment of immature necrotic teeth. These models would assist in assessing the impact of baghdadite and its combination with MTA on long-term vascularization, pulp-dentin complex formation, and functional regeneration results. Future investigations combining histological and molecular studies will prove invaluable in bringing these results towards clinical practice.

One of the significant considerations for clinical translation is determining long-term biocompatibility, mechanical stability, and degradation behavior of Baghdadite-MTA composites. Determining the nature and biological response to degradation products is critical to be able to predict long-term clinical behavior and to confirm safe and effective use in regenerative endodontics. In addition, determining the inflammatory response and immunogenicity potential of such biomaterials over long durations is important to define clinical safety and efficacy.

While this study centered on the biological function of Baghdadite, it is noted that commercial feasibility is a significant factor in clinical implementation. MTA, despite broad usage, is costly for its relative production and proprietary mix requirements. Baghdadite, as a synthetic silicate-based ceramic with scalable production capabilities, could provide a more cost-efficient option when standardized dental-grade compositions are commercially available. Nevertheless, as yet, Baghdadite is mainly reserved for experimental and biomedical research environments, and comparative costs of use in clinical contexts are as yet unavailable. Further research into cost–benefit ratios, especially when combined with MTA or other bio ceramics, would be informative in gauging its translational value in resource-constrained environments.

Conclusions

The present investigation makes a significant addition to the field by illustrating the increased angiogenic ability of Baghdadite and its synergistic effect when used in combination with MTA at optimal levels. The strong quantitative data generated through the use of the YSM assay illustrates the potential of these biomaterials

for application in clinical regenerative therapies with a focus on dosage and mixtures to achieve maximal therapeutic effect. Future research should aim at clarifying underlying biological processes, verifying these in more advanced pre-clinical and clinical models, and maximizing material properties for clinical application in regenerative endodontic treatments.

Conflicts of Interest

The authors declare no conflict of interest.

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