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Evaluating the Predictability and Regenerative Capacity of Novel Platelet Concentrate (PC)-Titanium Platelet Rich Fibrin (T-PRF) in the field of Dentistry- A Narrative Review

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Review

History

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ABSTRACT

Periodontal disease treatment is always a challenging task. Various treatment modalities have been applied for treating this painless chronic condition. With the advancement in the field of research in dentistry, researchers shifted towards autologous products hence came the usage of platelet concentrates in various branches of dentistry. Initially, fibrin glue and platelet-rich plasma (PRP) have been tried, but because of their drawbacks, platelet-rich fibrin (PRF) came into play. Due to possible contamination of silica particles in silica tubes or silica-coated plastic tubes and shorter resorption time, titanium attracted the researchers. This led to the introduction of titanium platelet-rich fibrin (T-PRF), a second-generation platelet concentrate. This had a thicker fibrin meshwork, better cellular entrapment, and greater resorption rate, and titanium tubes are inert, better hemocompatible, and non-corrosive. It also eliminates the possible contamination of silica test tubes and silica-coated plastic tubes. The present article is a review of T-PRF and its usage in the field of dentistry.

Key words: Periodontitis, Platelet Rich Fibrin, Platelets.

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Introduction

Periodontitis is a dysbiotic multifactorial disease that results in the destruction of the periodontium.[1] Regeneration of lost periodontal tissues is always a challenging task for a periodontist, how experienced and skill full he is may be.[2] Several non-surgical and surgical treatment modalities have been tried over several decades in order to treat these periodontal bone defects to achieve a firm and healthy periodontal structures along with regaining of lost alveolar bone and other periodontal structures.[3] Gradually, there has been a trend of incorporating several biomaterials like bone grafts and collagen membranes as a part of regenerative treatment strategies besides open flap debridement (OFD) alone.[4] During this search for better biomaterials, scientists came across platelet concentrates, which were considered a boon to dentistry as they were autologous and prepared from patients' own blood.

Initially, first, generation platelet concentrates (PC) like fibrin glue and platelet-rich plasma were introduced. But because of the use of bovine anti-thrombin, there might be some hypersensitivity reactions. Robust release of growth factors within the first half an hour after the insertion at the surgical site. This rapid release was not sufficient for the activation of progenitor and wound-healing cells of periodontal regeneration. Hence standard or leukocyte platelet-rich fibrin (S/L-PRF) and advanced PRF (A-PRF) were introduced, which were totally autogenous without anticoagulants.[5,6]

Initially Fibrin glue, Platelet Rich Plasma (PRP) were introduced, but because of the usage of bovine anti-thrombin as a part of activating platelets which might cause hypersensitivity reactions and robust release of growth factors within first half an hour of insertion at surgical site not sufficient for activation of cells for regeneration led to further research where Standard or Leukocyte Platelet Rich Fibrin (S/L-PRF), Advanced PRF (A-PRF) were introduced that is totally autogenous without anticoagulants.[5, 6]

For easy identification of PCs, they were categorized into generations. First generation – PRP, second generation-Leucocyte –PRF, A-PRF, injectable –PRF (i-PRF), pure-PRF (P-PRF) and Titanium-PRF (T-PRF). Some additional PC's are A-PRF+, Concentrated Growth Factors (CGF), etc.[7] Recently, Kobayashi *et al.*[8], introduced Albumenized PRF (Alb-PRF), where PRF clot was dipped in albumin gel. Based on centrifugation type another advancement happened which is called Horizontal PRF (H-PRF) by Miron *et al.*[9], but these advancements are under protocols with in-vitro studies, and much research is not performed on humans. Some protocols of various PCs are shown in Table 1.

Table 1. Shows the protocols of some of the platelet concentrates used in the field of dentistry

Platelet Concentrates	Centrifugation Protocol
Platelet Rich Plasma[18]	1st Centrifugation 3000rpm for 3 minutes 2nd Centrifugation 3000rpm for 13 minutes
Leucocyte- PRF[11, 19]	2700 rpm for 12 minutes; 3000 rpm for 10 minutes
Advanced PRF[20]	1500 rpm for 14 minutes
Injectable PRF[21]	400-700 rpm for 7-8 minutes 3300 rpm for 2-3 minutes
Titanium PRF[13, 15, 17]	2700 rpm to 12 minutes 3000 rpm for 10 minutes 3500 rpm for 15 minutes
Concentrated growth factors (CGF)[22]	30 seconds acceleration phase; 2 minutes- 2700 rpm; 4 minutes- 2400 rpm; 4 minutes- 2700 rpm, 3 minutes- 3000 rpm; 36 seconds deceleration phase and stop
Albuminized PRF[8]	Initially, blood was centrifuged for 8 minutes with 700 grams of rotational force. Platelet-poor plasma was gathered and heated at 75°C for 10 minutes to create denatured albumin gel. Then buffy coat and denatured albumin gel to form Alb PRF.
Horizontal PRF[23]	700 grams rotational force in a horizontal centrifugation machine for 8 minutes.

PRF acts as a scaffold with entrapment of platelets, several white blood cells (WBCs), holds various growth factors like vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), insulin-like growth factor (IGF) and epidermal growth factor (EGF), it also holds several stem cells. Thus collectively acts at the surgical site and helps in rapid wound healing and regenerating the periodontal tissues[11]. But the resorption rate of this S/L-PRF & A-PRF was only 7-11 days, and O'Connell stated the possible silica contamination during their centrifugation preparations in silica or silica-coated test tubes.[11, 12] So there was again a search by researchers for a better biomaterial in order to eliminate these drawbacks, and this led to the introduction of a third generation of platelet concentrate Titanium Platelet Rich Fibrin (T-PRF).[13] Articles were searched in PubMed/ Medline, Google Scholar, Ebsco, Embase, etc., and gathered information so that a detailed report could be prepared. To the author's knowledge, we have included almost all recent studies, including systematic reviews and meta-analyses. The present review article briefly and exclusively discusses T-PRF regarding its history, histological analysis, centrifugation protocols, and its usage in various areas of dentistry as well as periodontology.

History of T-PRF

Due to the drawbacks of first-generation PCs, where silica particles within the test tube may get entrapped, sediment during the centrifugation, and contaminate the sample made, the researchers go on a hunt for better biomaterial. During this search, titanium metal has gained their attention and led to T-PRF preparation. As it is already established that titanium is regularly used in the preparation of dental implants, in 2013, Tunali M *et al.*,[13] introduced this T-PRF where sterile titanium tubes grade IV were used for centrifugation of blood immediately after drawing from patients. Titanium is a better biocompatible, haemocompatible, non-corrosive, and can passivate itself into the titanium dioxide (TiO_2) layer on the inner surface of the tube. This TiO_2 layer will activate platelets in a similar manner to that of silica particles and help in thicker fibrin meshwork and denser membranes with greater cellular entrapment.[14] This titanium also plays a role in the activation of osteoblast cells and progenitor cells of periodontium during the process of osseointegration after implant placement. It is stated that the resorption time of T-PRF was 21 days which was demonstrated on rabbits by Tunali M *et al.*, 2013.[13, 14]

Centrifugation Protocols:

Tunali M *et al.*,[13] stated a standard protocol of 2700 rotations per minute (rpm) up to 12 minutes where they have reported a properly polymerized PC clot. Chatterjee A *et al.*,[15] standardized their own protocol of 3000 rpm for 10 minutes. All recent studies followed the standard protocol of Tunali M *et al.* Study was done by Bhattacharya HS *et al.*,[16] and Gummaluri SS *et al.*,[17] used the modified Tunali M *et al.*,[13] protocol and obtained the T-PRF clots at 3500 rpm for 15 minutes. The basic method of preparation was that after the obtainment of fresh blood from the antecubital vein, it was directly transferred to sterile titanium tubes (Figures 1 and 2) with no delay then it was centrifuged with the appropriate protocols. Similar to normal PRF, three layers were reported as the top layer was plasma, the middle layer was a fibrin clot along with a buffy coat, and the bottom layer of RBC clot.

Figure 1: Shows the Image of T-PRF tubes

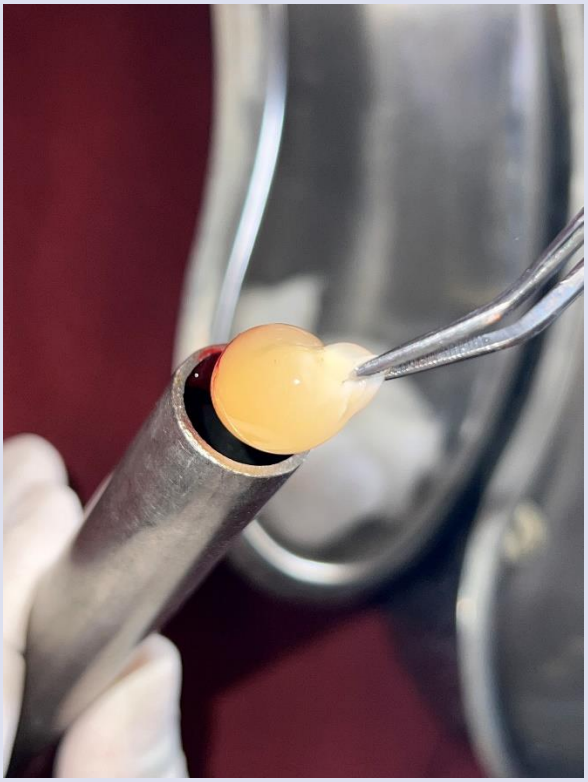

Figure 2: Shows the Image of the T-PRF clot retrieved from a titanium test tube.

Light Microscopic and Scanning Electron Microscopic Analysis

The structural and fibrin network pattern of T-PRF was evaluated by Tunali M *et al.*[13], where they concluded that T-PRF had a thicker fibrin meshwork with continuous integrity and covered a greater area of fibrin network than L-PRF. Further, in SEM analysis, a well-organized pattern with thicker fibrin meshwork and better entrapment of platelets were noted. Bhattacharya HS *et al.*[16], in their immune histochemical analysis, concluded that strong positive staining was reported for the distribution pattern of cells. For the labeling index also, positive staining was obtained for T & B- lymphocytes. Regarding localization of cells, positive staining was reported for platelets in T-PRF and for stem cells in L-PRF. A stronger significant positive staining regarding cell pattern was reported for neutrophils in L-PRF and B- lymphocytes in T-PRF. Further, Chatterjee A *et al.*[15], in their cell cytology study, stated that a thicker well-organized fibrin network pattern was recorded in T-PRF of healthy patients than in L-PRF. Hypertensive and smoker patients showed lesser fibrin border prominence in both the PC while adequate fibrin meshwork pattern was found in T-PRF clot when compared to L-PRF clot. These findings of thicker fibrin meshwork in T-PRF were also reported by Mitra DK *et al.*[24], in their histological evaluation.

Yajamanya SR *et al.*[25], in their cytology study, where the comparison between young and old age groups regarding fibrin network patterns of T and L-PRF stated that age plays a role in the quality and fibrin patterns of PRFs. Younger people have thicker fibrin meshwork and greater entrapment of red blood cells (RBC), platelets, and white blood cells (WBC) than older individuals. In older people, the pattern of PRFs was thin and loose, with less number of cells entrapped. Overall from the reports of the above studies, these histological evaluations are one mode of indirect evaluation for assuming the amount of healing and formation of new tissues after the placement of PCs at surgical sites. Thus T-PRF had better cellular entrapment with thicker fibrin meshwork and can hold an ample amount of growth factors which would stimulate the cells at the surgical site to recreate the lost tissues to as much extent as possible.

A recent study was done by Bhattacharya HS *et al.*[26], where histological sectioning of T-PRF and L-PRF was performed by collecting blood from 10 healthy volunteers. These T&L-PRF clots were subjected to processing according to protocols of Bancroft's manual and made into slides for LM analysis, and some clot samples were sent to SEM analysis. The results of their study concluded that there was no significant difference between T&L-PRF on histological analysis. SEM analysis also showed non-significance regarding fibrin thickness, cell entrapment, and structure, and significance was recorded in the body region of the clot. Thus. T-PRF can be a better alternative by eliminating the hazardous effects of silica.

Ravi S and Santhanakrishnan M[27], in their in-vitro study, compared T-PRF, L-PRF, and A-PRF, stated that T-PRF had high tensile strength, modulus of elasticity with greater time to degrade than L and A-PRF's. But the amount of release of GF, particularly PDGF AA, was rapid in T-PRF, while in A-PRF, it was a sustained release. Thus they concluded A-PRF as the most favorable PC for regenerative periodontal therapy

Uses of T-PRF in Dentistry

T-PRF applications in periodontal treatment

Various authors have utilized this T-PRF for the treatment of periodontal disease. Arabaci *et al.*,[28] used this T-PRF in the treatment of OFD, and the release of GF was observed. Results of the study stated that OFD+T-PRF helped in better soft tissue and surgical wound healing with lesser post-operative recession. Regarding GF's release, T-PRF had maintained a greater level of release of them up to 6 weeks post-operatively. Further, lesser levels of relative Receptor activator of nuclear factor kappa beta ligand/ Osteoprotegerin (RANKL/OPG) were reported, which indicated lesser post-operative bone loss and greater stabilization of surrounding periodontal tissues. Mitra DK *et al.*,[24] in their study concluded that both T and L-PRF groups had reduced probing depth (PD) and relative attachment levels (RAL) when compared from baseline to 9 months post-operative for intra-group comparisons, while on inter-group comparisons, both the groups showed no significant difference regarding the clinical and radiographic parameters of defect depth reduction.

A study was done by Paribas HG *et al.*,[29] where they utilized allograft as the control group, allograft+ T-PRF as the test group and assessed for PDGF-BB, VEGF-A, FGF-2, Anjiogenin (ANG), and Angiostatin (ANT) in gingival crevicular fluid samples at days 3, 7, 14 and 30th day. Where there was no significant difference regarding the release of these GF at all the time points, and T-PRF has no significant effects on angiogenic markers in the treatment of periodontal disease where bone grafts were treated with allograft+T-PRF. Chatterjee A *et al.*,[30] in their study treated the 90 intrabony defects in 38 patients by dividing into 3 groups, OFD alone, OFD+PRF and OFD+T-PRF and concluded that there was a significant improvement of decreased PPD, gain in CAL along with defect depth reduction 9 months post-operatively on comparison with OFD alone. While T-PRF+OFD and L-PRF+OFD showed no significant difference. Thus they concluded that both PC had shown improvements and could be used regularly for the treatment of periodontal disease.

In a study done by Gummaluri SS *et al.*,[17] treated 34 IBD with L & T-PRF and followed up to 9 months. They have concluded that both the groups have shown good improvements in clinical parameters indicated for soft tissue healing while T-PRF showed a more defect fill percentage indicating a greater hard tissue healing. They also stated that T-PRF can be a better alternative to L-PRF for treating IBDs.

A study was done by Ustaoglu G et al.,[31] on endo-period lesion-associated IBDs and stated that T-PRF had shown similar results with that of GTR membranes than OFD alone. Thus indicating that T-PRF can be used for the soft and hard tissue healing as an alternative to GTR membrane. A recent study done by Razi AM et al.,[32] used

PRF and T-PRF in 140 patients to manage endo-period lesions. They assessed the PPD and CAL at baseline 3 & 6 months and concluded that both the PC helped in good healing of the surgical site with no significant difference for inter-group comparisons, while intra-group statistical significance was reported from baseline to follow-up time periods.

Clinical pictures of T-PRF placement at surgical sites were depicted in Figure 3 and 4.

T-PRF application in treating gingival recession and assessment of palatal wound healing

Ustaoglu G *et al.*[33], also used T-PRF in palatal wound healing and histoconduction. In this, they used T-PRF clots and placed them at the donor sites where free gingival grafts were harvested and compared with the control group palatal site where no T-PRF clots were placed. In this palatal soft tissue thickness (PSTT) and wound healing of palatal mucosa, pain, bleeding, and post-operative consumption of painkillers were assessed. They followed up with the patients for up to 6 months and concluded that T-PRF helped in good palatal mucosal wound healing based on hydrogen peroxide bubble tests, significant color match scores at 1st and 2nd weeks, bleeding also reduced in the initial two days, and lesser intake of pain killers were noted in T-PRF group. There was no significant difference between baseline and 6-month follow-up of PSTT in the T-PRF group, while time-dependent thinning happened in the control group. They also concluded that T-PRF can be an alternative to sub-epithelial CTG (SCTG) because of its superior properties and equal functioning with that of SCTG.

Recent systematic review and meta-analysis done by Mahale SA *et al.*[34], stated that within limitations, T-PRF can be used for the treatment of IBD as it helped in reduced PPD and gain in CAL along with improvement in bone parameters. But the conclusions drawn were provisional because of a limited number of studies, shorter follow-ups, and histological evaluation was not performed that might indicate the actual amount of periodontal regeneration.

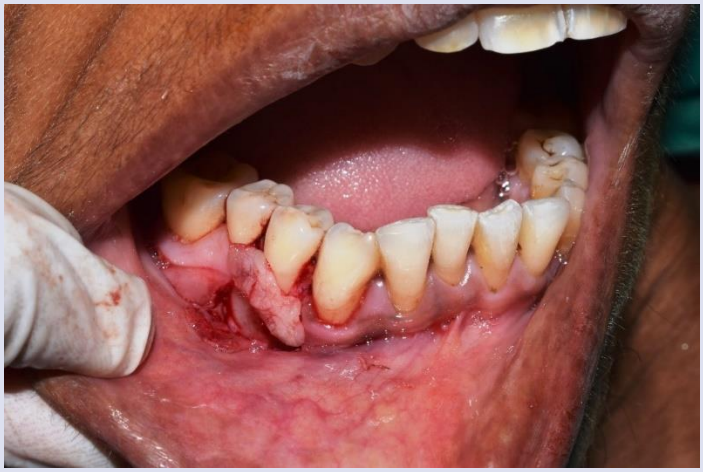

Figure 3: Shows the image of the T-PRF membrane placed in the intrabony defect

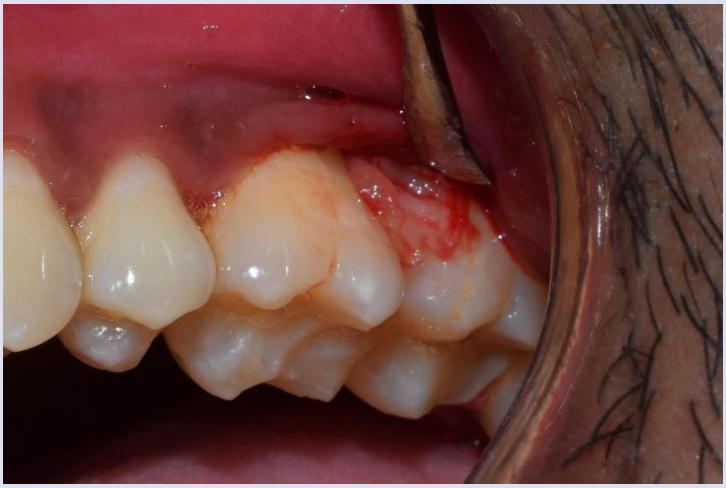

Figure 4: Shows the image of the T-PRF membrane placed on a gingival recession

Another systematic review done by Reshma AP *et al.*[35], also concluded that limited evidence was reported regarding the superiority of PRF over PRP and T-PRF over PRF for the treatment of osseous defects. There was no significant difference among the platelet concentrates. Hence the long number of randomized trials that would be published need to be considered and come to a proper conclusion.

At present, only a few randomized control trials have been performed regarding the usage of T-PRF as a biomaterial in the treatment of gingival recession. A study was done by Gummaluri SS *et al.*[36], and Ahmed S et al.,[37] where they treated Class I millers gingival recession with T-PRF as biomaterial using coronally advanced flap and modified coronally advanced tunneling technique (MCATT) and concluded that T-PRF is a good alternative biomaterial to connective tissue graft, eliminate the second surgical site and help in complete root coverage. Case report treated by Agarwal MC *et al.*[38], also stated that when T-PRF was used underneath the vestibular incision sub-periosteal tunnel access (VISTA) procedure in the anterior region helped in better healing and complete recession coverage of the surgical site. In a study done by Agarwal MC *et al.*[39], T-PRF was used as a biomaterial in pinhole surgical technique (PST) for the treatment of GR. During their follow-up periods, they concluded this PST was a conservative approach; it doesn't hamper blood supply, and patients experienced lesser post-surgical pain. Further, there was an increased post-surgical keratinized tissue width.

Koyuncuoglu CZ *et al.*[40], treated 62 miller class I/II gingival recessions using CTG and T-PRF with MCATT technique and followed up to 36 months where there was a root coverage with decreased recession depth, recession width and increased keratinized tissue width. They have concluded that T-PRF showed a similar amount of complete root coverage (80% and 56% for CTG at 6 months and 36 months, while it remained at 64% in T-PRF at 36 months) and acted as a good alternative treatment modality where the patient is not willing for a second surgical site.

Recent case series published by Bhattacharya HS et al.,[41] 2023 used T-PRF as a biomaterial underneath the coronally advanced flap for the treatment of Cairo type I recession defects. During their follow-ups, they concluded that T-PRF helped in the reduction of recession depth, recession width, and increased width of keratinized tissue with a mean root coverage percentage of 91%. They also stated that T-PRF eliminated the possible silica contamination and resulted in thicker fibrin membrane. Second surgical site preparation for SCT graft harvesting was also eliminated, as T-PRF recorded equal results with that of SCTG.[40]

T-PRF usage in Sinus Elevations and Dental Implants

Olgun E et al.,[42] compared the T-PRF with allograft in the treatment of sinus floor elevation, where they treated 18 posterior maxillary areas and randomly assigned 10 sites for T-PRF and 8 sites with allograft and followed up to 6 months. Radiographically allograft group showed better results, but histomorphometrically, T- PRF showed better bone formation, and it was accelerated to 4 months, and a greater time was reported with allografts. Thus they concluded that T-PRF alone usage in sinus operations had gained good histomorphometric and clinical results.

In implants, T-PRF was used by Ustaoglu et al.,[43] where it was compared with CTG. Soft tissue thickness (STT) and keratinized tissue width (KTW) were measured and compared at baseline and 3 months postoperatively. No significant difference was recorded for STT at the occlusal part of the alveolar crest measurement during inter-group comparison. During follow-up STT and KTW were increased, thus indicating T-PRF as an alternative to CTG in the treatment. Moreover, there was no crestal bone loss recorded in both T-PRF and CTG groups.

T-PRF as Drug Delivery System

This is one of the thrust areas where research will be performed in the near future. To the author's knowledge, only one study was published. Ercan E et al.,[44] compared T-PRF with Collagen Membrane loaded/injected with doxycycline gel. Further, anti-microbial efficacy and drug kinetics release for doxycycline. They have concluded that T-PRF holds the drug longer time and greater loading capacity than collagen. T-PRF loaded with doxycycline also had a thicker meshwork than collagen membrane on SEM images, it had long-term drug-carrying capacity, and the bibliophilic property of Doxy was mainly responsible for T-PRF's thicker fibrin meshwork.

T-PRF usage in Nerve conduction damage

Senturk F et al.,[45], in their study, utilized T-PRF in the treatment of facial nerve regeneration. It was an experimental study done on 27 male New Zealand rabbits. There were three groups. Where first group had a facial nerve dissected and left, while 2nd group had nerve dissection and suturing of that surgical site, and in 3rd group, apart from dissection & suturing, the T-PRF membrane was wrapped around the surgical area. Rabbits were followed up for 1, 3, 5, 7, and 10 weeks for whisker movements, motor reflexes, and lowering of ears. From their findings, they have concluded that T-PRF helped in partial nerve healing in both electrophysiology and functional levels.

Apart from this positivity, titanium tubes are costly; hence usage is still limited. On a brighter note, procuring them is like a one-time investment, and preparation of T-PRF at your clinical setup becomes much more regular as tubes are sterilizable and re-used.

Conclusions

Thus, within the limitations of this review, T-PRF can be a better alternative to L-PRF or A-PRF as it is autologous, eliminates the possible contamination of silica particles, Titanium metal is inert, non-corrosive, better haemocompatible, and activates platelets similar to silica particles. Thicker fibrin meshwork, longer duration of resorption, and greater holding of drug and sustained release made it an important biomaterial among PC and being regularly used in dentistry. It also eliminated the second surgical site and produced equal results with that of CTG. Further extensive research needs to be performed to establish ground-level firm evidence regarding its usage in the near future.

Acknowledgments

Nil.

Competing interests

Authors declare Nil conflicts of interest

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