



Effectiveness of Phytic Acid as an Etchant in Dentistry: A Systematic Review

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Eur J Gen Dent 2023;12:82–88.

Abstract

The aim of this study was to assess the effect of phytic acid and to compare it with the phosphoric acid etching through a systematic review. systematic search was carried out using PubMed/MEDLINE, Cochrane library, Indmed, Scopus, and Liliacs databases conducted upto January 2022. In vitro studies comparing phytic acid and phosphoric acid as an etchant on tooth surfaces that performed bond strength, smear layer removal, collagen degradation and monomer penetration were included. The risk of bias was assessed considering Checklist for Reporting In-vitro Studies guidelines. Five studies were chosen for full-text assessment out of 830 that were potentially eligible. The studies found that phytic acid improved bond strength, collagen degradation, smear layer removal, and monomer penetration. Every study had a moderate-to-high risk of bias. Phytic acid enhanced the etch and rinse adhesive's binding strength to dentin, effectively eradicated the smear layer, protected dentin collagen from degradation, and had better resin infiltration and minimal effect on pulpal cells.

Keywords

- ▶ acid etching
- ▶ etchant
- ▶ phytic acid
- ▶ phosphoric acid

Introduction

Concepts in restorative dentistry have been continually developing, and adhesive dentistry has gained increasing importance. Adhesive systems achieve micromechanical retention using acid etch technique. This provides acceptable retention by selectively eroding hydroxyapatite by providing irregularities that aid in increasing the adhesion of restorative materials. Acid etching results in demineralization of intact subsurface dentin by complete smear layer removal, leaving a moist collagen-rich surface into which resin diffuses to form a hybrid layer. The most widely used etchant is 37% phosphoric acid (PA) for 15 seconds.¹ PA has an effective bonding to enamel but has an aggressive nature toward dentin,² because the exposed collagen fibers are fragile and devoid of hydroxyapatite crystals. Their bonding to dentin was compromised leading to reduced bond strength,

postoperative sensitivity, and incomplete penetration of resin.³ Furthermore, PA alters the interaction of proteinases in dentin, improving the durability of resin-based biomaterials in peril. To reduce the activity of enzymes on dentin by PA, various cross-linking agents such as ethylenediaminetetraacetic acid (EDTA), maleic acid, lactic acid, or citric acid have been used. These disadvantages of PA make it a better acid for etching tooth surfaces.

In 1872, Pfeffer discovered phytic acid, commonly called inositol hexakisphosphate or inositol polyphosphate (IP6), a phosphorus storage form in plant seeds. Phytic acid has distinct properties owing to its large negative charge and ability to bind positive ions to form compounds that are dissolved in acidic conditions and precipitate at neutral pH.⁴ IP6, which has an anticariogenic property, has a positive influence on reducing the dissolution of enamel.⁵ Studies on phytic acid have resulted in a significant increase in bond

article published online
September 6, 2023

DOI <https://doi.org/10.1055/s-0043-1770986>.
ISSN 2320-4753.

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strength, effective removal of the smear layer, and negligible impact on pulpal cells at lower concentrations when compared with PA. The tendency of IP6 to form undissolved complexes that provide collagen stabilization is the proposed mechanism of action behind the increased bond strength.

Several *in vitro* studies have been conducted to assess the efficacy of phytic acid as an etchant. With the growing use of phytic acid as an etchant, a thorough evaluation of all *in vitro* studies with phytic acid is required to guide its use. Systematic reviews on *in vitro* studies allow mapping and synthesizing evidence about newer approaches that can be considered for clinical use as well.⁶⁻⁸ However, *in vitro* studies increase transparency and address the significance of clinical translation; it enhances the safety and efficacy of treatment in clinical practice. Hence, this systematic review is aimed to compare the efficacies of newer phytic acid with that of the standard PA.

The primary objective of this systematic review was to summarize the research on acid-etching protocols for adequate resin adhesion and to demonstrate the differences between the available evidence of phytic acid and PA as an etching agent.

Methods

The systematic review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The following PICOS framework was used: population, human teeth; intervention, phytic acid; control, PA; outcome, bond strength, smear layer removal, collagen degradation, and monomer penetration; and study design, *in vitro* studies. The research question was: "Is phytic acid a potential etchant?"

Information Sources

The protocol of this review was registered as CRD4202127200 in the International Prospective Register of Systematic Reviews (PROSPERO), and can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021272001

Literature Search

Two reviewers independently conducted the literature search until May 2022. For related papers, a comprehensive literature search was conducted using PubMed/MEDLINE, Cochrane Library, Indmed, Scopus, and Liliacs. The keywords and MESH Terms used in PUBMED were as follows: (((("phytic acid"[MeSH Terms] OR ("phytic"[All Fields] OR "inositol hexaphosphate"[All Fields]) OR "IP6"[All Fields]) AND ("demineralization"[All Fields] OR "demineralizing"[All Fields] AND "enamel"[All Fields]) OR "dental enamel"[All Fields] AND "etching"[All Fields] AND (("dentin"[MeSH Terms] AND ("smear layer"[MeSH Terms] OR "smear layer"[All Fields]) AND ("collagen"[MeSH Terms] OR "collagen"[All Fields] AND ("stable"[All Fields] OR "stabilization"[All Fields] OR "stabilize"[All Fields] AND ("resin"[All Fields] AND ("infiltrate"[All Fields] OR "infiltrated"[All Fields] AND ("microtensile"[All Fields] AND "bond"[All Fields] AND ("strength"[All Fields] OR "strengths"[All Fields])))). This search was accompanied by manual search for additional literature in relevant references.

The search results were imported to Mendeley Desktop (version 1.18.9) to locate and remove duplicates.

Study Selection

Two authors independently examined the titles and abstracts to identify studies that met the following criteria: (1) *in vitro* studies investigating the effects of IP6 as an etchant on enamel or dentin; (2) studies evaluating adhesion strength, smear layer removal, collagen stability and resin infiltration; and (3) PA studies on bond strength, smear layer removal, dentin collagen stability, and resin infiltration. Studies that used criteria other than those stipulated in the inclusion criteria were excluded. Case reports, *in vivo* studies, and reviews were not included. Full-text manuscripts that met the inclusion criteria were chosen for further evaluation. Disagreements on eligibility between the two authors were sorted with the help of a third reviewer.

Data Extraction

The data recorded included the first author's name, country of publication, year of study, type of tooth, type and concentration of etching agent used, etching time, standard deviation of bond strength in each group, effect on smear layer, collagen degradation, and monomer penetration.

Quality Assessment

The risk of bias of all *in vitro* studies was assessed according to the following parameters based on the Checklist for Reporting In-vitro Studies (CRIS) guidelines:

1. Specimen randomization
2. Sample size calculation
3. Similar number of teeth per group
4. Failure mode evaluation
5. Operator blinding
6. Standardization of sample preparation.

If the authors recognized the parameter, a "YES" was assigned; otherwise, it was assigned a "NO." The risk of bias was estimated by adding the number of parameters that assigned a "YES": 1 to 3 indicated a high risk of bias; 4 to 5 indicated a medium risk; and 6 to 7 indicated a low risk.

Results

Study Selection

PRISMA flowchart summarized the study selection procedure (► **Fig. 1**). From all databases, 830 articles were found. Two articles were included in the manual searches. After examining 830 studies for title screening, 74 were chosen for abstract screening based on the inclusion criteria. Three studies were selected for the full-text screening. Most of the other studies were excluded due to the exclusion criteria. Consequently, the qualitative analysis included five studies.

Descriptive Analysis

The study characteristics and outcomes are summarized in ► **Table 1**. All studies were conducted in Japan. All of the studies were published between 1991 and 2022 in English.

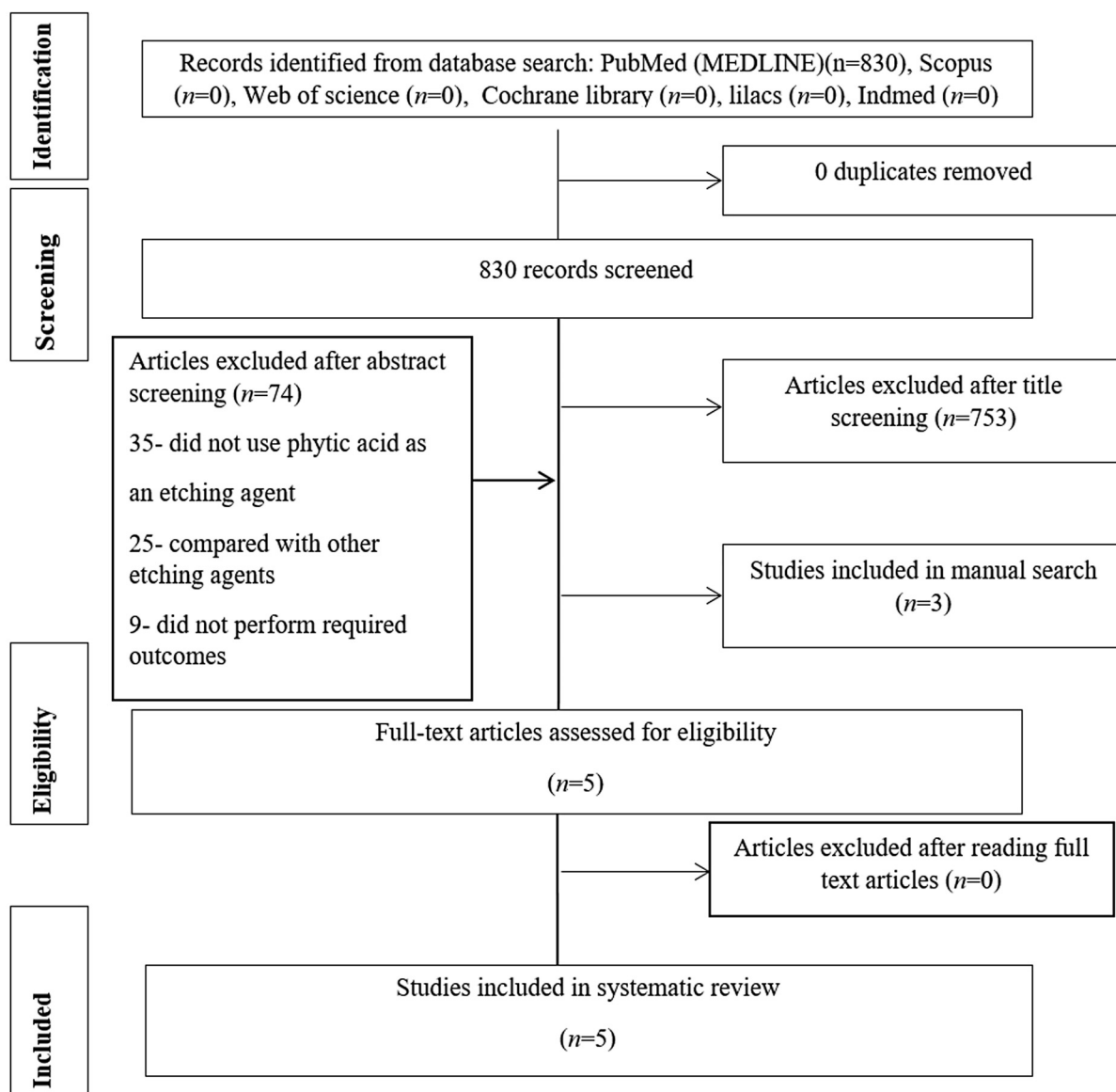


Fig. 1 Flowchart diagram of study selection according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Microtensile bond strength tests were performed in four studies. Three studies evaluated the effect of the etchant on smear layer removal, three evaluated the effect on collagen degradation, and one evaluated monomer penetration.

Risk of Bias and Quality of the Studies

All included studies had high risk of bias (►Table 2). However, several studies failed to provide information on calculation, randomization, single operator, and operator blinding.

Discussion

Acid etching is among the most effective methods to promote retention by selectively eroding hydroxyapatite and producing irregularities that aid in increasing the adhesion of restorative materials. In 1955, Buonocore postulated an acid etch technique. He discovered that enamel etching created a relatively small porous surface into which resins

flowed and polymerized, resulting in micromechanical retention. They reported that the application of 85% PA to enamel improved the adhesion of resin restorations. Since then, PA etching of enamel has been routinely performed. The success of bonding to enamel led to acid etching of the dentin.⁹

Unlike enamel, bonding to dentin presents a greater challenge owing to its composition and the presence of a dense network of tubules that connects the pulp with the dentin-enamel junction. One goal of dentin etching is to remove the smear layer and allow the dentin matrix to bond directly. Van Meerbeek et al (2020)¹⁰ were the first to identify the potential applicability of PA for dentin etching, smear layer removal, and subsequent restoration with an adhesive resin. However, when dissolved in PA, the mineral phase of smear layer reveals a collagen network with adhesive materials that fill the spaces within the collagen fibrils, resulting in hybrid layer. PA depletes the hydroxyapatite in

Table 1 Demographic data of the included studies

Study	Country	Type of teeth	Mechanical test	Etching agent		Etching time	Variables assessed		
				Control	Study		Bond strength (SD) (MPa)	Smear layer removal	Collagen degradation
Nassar and Islam 2021 ²⁴	Japan	Permanent molars	Microtensile	65% PA	Study	30 s	IP6 effectively removed the smear layer similar to PA	-	-
						30 s			
						30 s			
Forgione et al 2021 ²³		Permanent molars	-	37% PA	Study	30s	-	IP6 treated dentin showed less total dentinal collagen degradation than PA	-
						1 min			
						1 min			
Kong et al 2016 ¹³	Japan	Permanent molars	Microtensile	35% PA	Study	15 s	IP6 effectively removed the smear layer similar to PA with thin demineralized layer than PA	PA showed increased degraded collagen and IP6 shows very less changes	IP6 showed better resin infiltration with less nanoleakage when compared with PA
						30 s			
						30 s			
Kong et al 2015 ²⁶	Japan	Permanent molars	Microtensile	37% PA-wet 37% PA-dry	Study	15 s	-	PA showed severe aggregation of collagen and IP6 treated dentine showed well-preserved collagen	-
						15 s			
						30 s			
Nassar et al 2013 ³	Japan	Permanent molars	Microtensile	37% PA	Study	15 s	IP6 effectively removed the smear layer than PA	-	-
						60 s			
						30 s			
						15 s			

Abbreviations: IP6, inositol polyphosphate; PA, phosphoric acid; SD, standard deviation.

Table 2 Risk of bias according to CRIS guidelines

Study	Random sequence	Sample size calculation	Same number of teeth per group	Failure mode evaluation	Single operator	Blinded operator	Standardization of sample preparation	Risk of bias
Nassar and Islam 2021 ²³	Yes	No	No	Yes	No	No	Yes	High
Forgione et al 2021 ²²	Yes	No	Yes	No	No	No	Yes	High
Kong et al. 2016 ¹²	Yes	No	Yes	Yes	No	No	Yes	Moderate
Kong et al 2015 ²⁵	Yes	No	Yes	Yes	No	No	Yes	Moderate
Nassar et al 2013 ³	Yes	No	No	Yes	No	No	Yes	High

Abbreviation: CRIS, Checklist for Reporting In-vitro Studies.

the collagen network, causing it to collapse when dry and preventing the effective penetration of the adhesive. Several approaches to overcoming this problem with two-step etch-and-rinse adhesives have been proposed, the first of which was the “wet-bonding process,” which uses ethanol or water. However, these methods have various drawbacks.^{11,12}

Phytic acid shows increased negative charges because of its six phosphate groups, which become ionized at normal pH, where the negative charges are mitigated by mostly by sodium ions. According to previous studies, IP6 has maintained a balanced level of interest because of its ability to entangle hydroxyapatite to form a monomolecular surface layer that restricts both hydroxyapatite crystal dissolution and growth, thereby impairing plaque formation, caries, and enamel disintegration.

Kong et al discovered that IP6 has an advantage as an etchant because it removed the smear layer with better resin infiltration and, less nanoleakage and concurrently stabilizes the exposed collagen through its cross-linking activity. The action of a cross linking agent is to maintain collagen in an inflated state, causing irreversible loss of flexibility. Researchers have found that IP6 increases the bond strength of demineralized dentin while also preventing collagen fibril collapse. According to Kong et al,¹³ phytic acid showed higher resin dentin bonding strength compared to that of PA, and resin infiltration was better with IP6 than with PA based on nanoleakage, but various other studies have evaluated the monomer depth with analytical techniques such as stereo-microscopy or cross-polarized light microscopy that can improve the accuracy of the assessment.^{14,15}

The increased bond strength of dentin obtained with IP6 can be explained by a variety of mechanisms. First, IP6 can form insoluble compounds with calcium at pH levels greater than 4. Owing to the high buffering capacity of dentin, these complexes are expected to form despite IP6's low acidity.¹⁶ The insoluble IP6-calcium complexes may provide structural stability to the exposed dentinal collagen network, enhancing monomer infiltration and bonding to the dentin. Binary or ternary interactions between IP6 and collagen also increase collagen stability. IP6 crosslinks collagen via an electrostatic interaction, resulting in a binary association between the negatively charged IP6 and the dentinal collagen network, which may acquire a positive net charge upon acid exposure. A ternary interaction between IP6 and collagen may also occur, in which a cation such as calcium bridges IP6 with collagen. This type of interaction occurs when pH is higher than the isoelectric point of collagen.¹⁷

Ideally, the collagen network of demineralized dentin should be resin infiltrated and polymerized, resulting in a consistent resin/collagen network capable of stabilizing the restoration to dentin. However, the insufficient infiltration of monomers into the collagen network of acid etched dentin renders unprotected collagen fibrils vulnerable to host-derived enzymatic degradation.

Matrix metalloproteases (MMPs) and cysteine cathepsins are endogenous host proteases found in the pulp complex and dentin affected by caries, which facilitate the release of carboxyterminal telopeptide of collagen

type I and c-terminal telopeptide of collagen type I during collagen type I degradation.^{18,19}

Dentin etching with PA induces the activation and modulation of proteolytic enzymes in a concentration-dependent manner. Solvents, antimicrobial agents, cross-linking agents, and ethanol wet-bonding techniques have been proposed to reduce the enzymatic activity induced by PA on dentin.^{12,20}

MMPs require calcium and zinc to preserve their structure and active site; thus, chelation of zinc and calcium is a proposed mechanism for lowering dentinal MMP activity, and agents that work through this mechanism are considered first generation inhibitors of MMPs.²¹ The ability of phytic acid to chelate zinc and calcium is remarkable. Various factors influence the solubility of calcium-phytic acid compounds, including the phytic acid-to-cation ratio and pH. These compounds are dissolvable at low pH but insoluble at higher pH levels (> 4).¹⁶ Phytic acid can also interact with various enzymes (such as proteinases), and the majority of these interactions result in a decrease proteolytic activity.²² The interplay between phytic acid with amino groups is also a factor in reducing tissue degradability by obstructing and protecting the collagenase cleavage site. The compounds formed as a result of this interaction are more resistant enzymatically, necessitating higher enzyme concentrations for their degradation.^{17,23}

Phytic acid can act as a Hofmeister anion, which stabilizes proteins by direct interaction with water, resulting in a kosmotropic effect.¹⁷ According to recent studies, IP6 treatment of dentin results in less dentinal collagen degradation than that associated with PA treatment. The lower percentage of dentin adhesive failures in the IP6-treated dentin may be due to the enhanced stability of the exposed collagen network caused by the kosmotropic effect of IP6.²³

Kong et al compared PA, EDTA, and IP6 and discovered that IP6 completely removed the smear layer and smear plug by gently etching the dentin, but EDTA and PA demineralized the dentin and caused delayed collagen degradation. Despite the slight etching effect on dentin, IP6 was associated with higher bond strength. Furthermore, IP6 inhibited bacterial collagenase degradation.

An ideal etch pattern is not required to produce a high bond strength with enamel; however, excessive etching, whether by increasing the concentration or the application time of the etchant, would result in compromised bonding to enamel owing to the decrease in hardness of the substrate. Nassar and Islam showed that etching enamel with 1 and 5% IP6 had no better results than that attained by etching with PA, whereas 10% IP6 reduced the bond strength of the resin cement to enamel. IP6 is a stronger acid than PA and contains six phosphate groups, each with two dissociable OH groups. Consequently, 10% IP6 provides lower bond strength than that associated with PA owing to excessive demineralization and enamel hardness. Furthermore, compared to PA, 1% IP6 causes significantly less enamel surface erosion.²⁴

The hypothesis evaluated in this review was accepted because IP6 effectively etched dentin and eliminated the smear layer, resulting in excellent bond strength values with low nanoleakage, dentin dry mass loss, and collagen degra-

ation.¹³ Moreover, a cell line study with rat pulpal cells showed insignificant changes with usage of phytic acid, whereas PA significantly reduced their viability as it damages the DNA in human lymphocytes.²⁵

The review of only in vitro studies was a limitation of this study. All included studies had a moderate- to-high risk of bias based on the CRIS guidelines to standardize the reporting of in vitro studies. The lack of details such as sample size calculation, specimen randomization, and blinding of operator performing the mechanical tests, as well as the constraints, should be examined in future studies. The methodological constraints of these in vitro investigations prevent their direct extrapolation to the clinical condition. Moreover, due to methodological variances, meta-analyses were not performed. Future in vitro investigations should simulate the oral environment, which may alter the bond strength of IP6. Moreover, extensive analysis and comparisons of IP6 and PA, their effects on the chemical and physical properties of enamel, bonding quality, microleakage under different conditions that simulate clinical situations followed by in vivo studies using randomized control trials should also be conducted.

Conclusion

This study identified significant differences in bond strength, smear layer removal, and collagen degradation when phytic acid was used as an etchant versus PA; however, the included in vitro studies methodological limitations with a moderate-to-high risk of bias necessitate additional research before it can be implemented as an alternative to PA. Within these limitations, this systematic review revealed the insight of IP6, a unique natural compound with the potential to substitute PA for tooth surface etching.

Conflict of Interest

None declared.

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